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⑤ proteins ⑥ fats ⑦ water
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⑩ vitamins ⑪ nutrients
foods ⑬ cereals ⑭ food
ns ⑮ nutritional diseases
man diseases

⑰ dietetic treatment
⑱ public health
⑲ diet ⑳ physiological
㉑ nutritional
stress
disorders.

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HUMAN NUTRITION AND DIETETICS

BY

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SECOND EDITION

Dietetian

2ND EDN

E. & S. LIVINGSTONE LTD.
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1963

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FOREWORD

WHEN in 1939 I was asked by Sir Stanley Davidson and Dr Ian Anderson to write a foreword to their textbook of dietetics I gladly agreed. The book brought the newer knowledge of nutrition to the medical student, general practitioner and dietitian of that time. As I said then, " there must be a time lag between the acquisition of fundamental scientific knowledge in the laboratory and its application to human medicine. . . . The time lag in the past has been too long. . . . There is a need for closer co-operation between the research worker and the clinician." This is still true to-day. When I was Director of the Rowett Research Institute, Aberdeenshire, I had frequent opportunities to see remarkable advances in the field of animal nutrition which only much later found their application in clinical practice.

Research in nutrition—which has made such a great contribution to medicine by elucidating the cause, cure and prevention of deficiency diseases—continues to yield results of practical value in the treatment of diseases not primarily due to faulty diet. The general background of the newer knowledge of nutrition which this book gives will enable the clinician to appreciate the significance of these advances in this increasingly important aspect of medical practice.

I am glad that this new book deals with the world food problem. Although the advance in the science of nutrition has given us the knowledge of the kind of diet needed for health—and the advance in agricultural science enables us to produce food in abundance—about half the people in the world suffer from malnutrition and at times from hunger. The medical profession has some responsibility for this maladjustment. The reduction in the death-rate due to the elimination of disease in under-developed countries without a corresponding reduction in the birth-rate has led to a greater increase in population than in food production. The chapter dealing with these problems will be appreciated by members of the medical profession who take an interest in the long-term changes in the social order being brought about by the advances of medicine.

This book gives in lucid language and in one volume the knowledge needed for the application of recent research in nutrition ; hence it can be strongly recommended.

BOYD ORR.

PREFACE TO THE SECOND EDITION

SINCE the publication of the last edition we have to record with deep regret the tragic accidental death, while fishing, of our colleague, Dr A. P. Meiklejohn. We have therefore undertaken the task of revising and bringing up to date those sections of the book for which he was mainly responsible.

The excellent reception of the first edition has convinced all concerned in its publication that the policy on which it was based was a sound one. Accordingly this policy, which is fully explained in the preface to the first edition, has been maintained.

Every section of the book has been carefully revised and the chapters on Fats, Food Poisons, Starvation, Obesity, Kwashiorkor, Osteomalacia and Osteoporosis, Diseases of the Cardiovascular System, Diabetes, and Pregnancy, Lactation and Childhood have been completely rewritten.

Two new chapters have been added, namely Inborn Errors of Metabolism, and Nutrition and Care of the Aged. One chapter has been deleted, namely Nutrition and Malignant Disease. Much of the material from this chapter has been incorporated in the chapter devoted to poisonous chemical substances in foods.

In the first edition the diet sheets were in apposition to the description of the diseases for which they were primarily constructed. This tended to break the continuity of the reading matter. In addition some diet sheets were recommended for the treatment of clinical features such as œdema, obesity, nitrogen retention, etc., which can occur in a variety of disorders of widely differing ætiology. Accordingly we have now grouped the 23 diet sheets together in an appendix at the end of the book.

We have much pleasure in acknowledging the expert help and advice which we have received from many friends and colleagues in the University of Edinburgh and elsewhere. Many valuable suggestions have been received, most of which have been accepted ; it has not been possible, however, to incorporate all of them, otherwise the book would have been greatly increased in size. We are particularly indebted to Dr Bruce Nicol who, after many years in Africa as a member of the Colonial Medical Service, is now Deputy Director of the Nutrition Division of FAO in Rome.

We also wish to express our thanks for the advice we have received from Sir Dugald Baird, Dr G. S. Boyd, Dr L. J. P. Duncan, Professor R. W. B. Ellis, Dr J. W. Farquhar, Professor R. H. Girdwood, Professor R. J. Kellar, Dr Michael Oliver, Dr John Richmond and Dr J. S. Robson, and to Miss Kathleen Rose, Senior Dietitian, Edinburgh Royal Infirmary, who has kindly helped with all the diets.

We wish to thank the authors who have allowed us to use their illustrations and figures. The following editors and publishers have kindly given us permission to reproduce material of which they own the copyright : *British Journal of Nutrition*, *Journal of Physiology*, *Quarterly Journal of Experimental Physiology*, *American Journal of Physiology*, *Biochemical Journal*, *Lancet*, *British Medical Journal*, *British Medical Bulletin*, *Indian Journal of Medical Research*, *South African Medical Journal*, *Acta Medica Scandinavica*, *New England Journal of Medicine*, *Archives of Dermatology and Syphilis*, *Evening Standard*, *Atlantis*, *New Scientist*, E. & S. Livingstone Ltd., Oliver & Boyd Ltd., John Smith & Son (Glasgow), Cambridge University Press, McGraw-Hill Book Co. Inc., Her Majesty's Stationery Office, the Wellcome Museum of Medical Science, the Iodine Education Bureau, the Government Information Offices (Tanganyika and Kenya), and FAO Information Office.

We also wish to thank Mrs Mona Wilson for the care and accuracy with which our MSS has been typed and for help in reading the proofs, and finally, to thank our publishers, E. & S. Livingstone Ltd., for their kindly assistance and invaluable advice throughout the preparation of this book.

STANLEY DAVIDSON.
R. PASSMORE.

January 1963.

PREFACE TO THE FIRST EDITION

In 1940 one of us (S. D.), with Dr Ian Anderson, published *A Textbook of Dietetics*. This was based on lectures given to medical students at Aberdeen University and was designed to aid British general practitioners in treating and preventing disease by dietetic measures. Since then, great developments have taken place in the science of human nutrition. The application of this science has spread far beyond the field of clinical practice and is now recognised to be vitally important in many public health problems, as Lord Boyd Orr forecast in his foreword to the first edition of the *Textbook of Dietetics*.

Since many people now realise the importance of good food in adequate amounts for the preservation of health, and the value of suitable diets for the treatment of disease, it seemed to us that a new book on human nutrition and dietetics was needed. Our intention has been to set out the whole wide subject of human nutrition in proper perspective and to bring its many aspects together into one volume.

If asked " Who is this book for ? " we would reply : " For anyone interested in applying modern scientific knowledge to the practical problems of human nutrition, both in health and disease." This includes people in many different walks of life.

General practitioners, physicians and surgeons are responsible for seeing that their patients are provided with diets that are most suited for promoting health and aiding recovery from illness. Medical students may find that this book will help them to co-ordinate their knowledge of the physiological, biochemical, clinical and public health aspects of human nutrition. The doctor, in whatever branch of medicine he practises, ought to have a general understanding of the viewpoint of physiologists and food technologists, and *vice versa*. Dietitians and nurses must see that the doctor's dietary prescription is translated into a menu providing meals that are eaten and enjoyed by the patient. For this they need to maintain close and cordial co-operation with the hospital catering officer. Public health doctors and food administrators have the duty to ensure that supplies of food are available, adequate both in quantity and quality, for the needs of the people. Food technologists—chemists, millers, refrigerating engineers and others—must make certain that the methods they use for processing food do not spoil its nutritive value. Farmers and other food producers may well wish to know how the goods which they produce and sell contribute to essential human needs. For people in all of these categories some understanding of the modern science of human nutrition is invaluable.

In recent years nutritional science has advanced in many directions and has sometimes become so highly technical that it is often difficult for an expert in one particular field to view his work clearly in relation to other closely allied developments. There is thus a danger that misunderstandings and misdirected efforts may hinder measures for providing food adequate to sustain the health of mankind.

As doctors we have written this book in the language and style familiar to medicine; nevertheless we hope it will be intelligible to non-medical people professionally concerned with the subject. For this reason we have tried, as far as possible, to avoid obscure technical medical terms. Our aim has been to make most of the text understandable to any interested reader with a background of general scientific education.

The book is divided into six parts.

Part I gives an account of the physiology of nutrition. It is somewhat longer and more complete than the accounts found in most standard textbooks of physiology.

Part II gives a general description of the foods most commonly eaten by man. Their chemical and nutritive properties are described, as are the effects of food processing—milling, preserving and cooking. A short account is given of the various forms of food poisoning.

Part III describes in detail those diseases that are known to be primarily due to faulty nutrition.

Part IV deals with the role of defective diets in contributing to the onset of general diseases which are not primarily nutritional in origin. An account is given of the dietetic treatment of the principal diseases in which diet is of undoubted therapeutic value.

Part V is concerned with nutrition in relation to public health. The various measures available (especially in times of crisis) for ensuring an adequate supply of food are discussed. This part includes an account of the work of the Food and Agriculture Organization of the United Nations (FAO) and of other international bodies concerned with human nutrition. A chapter on the population problem is included.

Part VI deals briefly with the modifications necessary in normal diets to meet the special circumstances of pregnancy, lactation, childhood, athletic training and climatic extremes. Rations for expeditions and emergencies (such as shipwreck) are also discussed.

Numerous tables showing the nutritive values of different foods will be found in Parts I and II, while twenty diets recommended for the treatment of various diseases, and a table of suitable dietary exchanges, have been inserted at appropriate points in the text of Parts III and IV.

In presenting this book our hope is that we have been able to show that the business of feeding people now rests on a sound scientific basis, and that the study of human nutrition deserves recognition as a proper academic discipline.

STANLEY DAVIDSON.
A. P. MEIKLEJOHN.
R. PASSMORE.

January 1959.

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PART I—PHYSIOLOGY

CHAPTER 1

THE COMPOSITION OF THE BODY

What are little boys made of ?
What are little boys made of ?
Slugs and snails and puppy-dogs' tails ;
That's what little boys are made of.

What are little girls made of ?
What are little girls made of ?
Sugar and spice and all things nice ;
That's what little girls are made of.

MANKIND has always been interested in food. This, though a platitude, is worth remembering. The practice of dietetics is an ancient, empirical and sometimes elegant art. It is only in the last fifty years that it has also become a science. To-day, for the first time in history, there is sufficient scientific knowledge to give a reasonable account of why a man needs food and what he does with it. That is our justification for writing this book. Any account of this subject must begin with the essential question : what is man made of ?

Many carcasses of small animals have been analysed chemically, but the results do not necessarily apply to man. A complete chemical analysis of the human cadaver is a formidable task which has been carried out on a number of occasions, but not sufficiently often to give the range of variations in people of different age and sex (Widdowson *et al.*, 1951). Nevertheless, enough is known to state that the data in Table 1, 1 are representative of a normal man.

TABLE 1, 1. *A normal chemical composition for a man weighing* 65 *kg.*

	Kg.	Per cent.
Protein	11·0	16·9
Fat	9·0	13·8
Carbohydrate	0·5	0·8
Water	40·0	61·6
Minerals	4·5	6·9

Most of the material listed in Table 1, 1 is part of the essential structure of the body, but a portion represents reserves or stores. Of the 9 kg. of fat not more than about 1 kg. is essential ; the remainder represents a store which can be drawn upon in times of need. In obese people this store may be very much larger and form up to 70 per cent. of the body weight. Most of the protein is an essential component of the cells, but there is some reserve; probably about 2 kg. can be lost without serious results. By contrast, the body can be depleted at most by 200 g. of carbohydrate. During starvation the store of carbohydrate is continually replenished by synthesis from the larger reserves of protein and fat. The body can lose about 10 per cent. of its total water and at least a third of the mineral content of the skeleton without serious consequences. The size of the stores and the factors that determine deposits and withdrawals are most important nutritional considerations, which will be amplified in succeeding chapters.

THE COMPARTMENTS OF THE BODY

The materials that compose the body, as listed in Table 1, 1, are distributed through four separate compartments which together comprise the chemical anatomy of the body. These are:

1. The cells.
2. The extracellular fluid.
3. The mineral skeleton.
4. Adipose tissue.

It is possible to investigate this distribution in living man by indirect means. An excellent review of the subject with an account of recent developments in both the theory and practice of human chemical anatomy is available (Brozek & Henschel, 1961). Some of the methods used for this purpose and their results are as follows.

Body water

The 40 *l.* of water in the body are in two parts. The larger (about 25 *l.*) is present within the cells and the smaller (about 15 *l.*) is extracellular—in the tissue spaces, blood and cerebrospinal fluid. In living man or any intact animal it is possible to estimate the total body water in the following way. A known weight of a substance which is freely diffusible in all the body fluids is given to the subject, either by mouth or by intravenous injection. After sufficient time has been allowed for the substance to diffuse throughout all the tissues, a sample of blood is withdrawn and the concentration of the substance in the plasma determined. Then from the extent of the dilution of the substance in the plasma, the total body water can be calculated. Corrections have to be made for any excretion or metabolism of the substance during the period of diffusion. Many freely diffusible substances have been used for this purpose. Urea, antipyrine and the isotopes, deuterium and tritium, have been most often employed. Consistent results with each have been obtained by experienced workers. Each substance requires either expensive apparatus or considerable analytical skill for its determination. Consequently these methods can be carried out only in well-equipped research laboratories and are not undertaken routinely in hospital practice. There is also the dual assumption not only that the test substance is freely diffusible into all cells of the body but also that proper corrections have been made for any losses. For these reasons the prudent sometimes express their results in terms of the size of the ' urea space ' or the ' antipyrine space.'

It is possible to measure the extracellular fluid by determining the dilution in the plasma after injection or ingestion of a substance which is freely diffusible in the tissue spaces, but which does not enter the cells. Sucrose, inorganic sulphate and sodium thiocyanate appear to occupy the same ' space ' in the body, which is probably the same as the extracellular fluid. The ' thiocyanate space ' can be measured conveniently in any laboratory without special equipment, and provides a useful measure of the extracellular fluid. (Thiocyanate enters the red blood corpuscles and a correction has to be made in calculating the extracellular fluid from the thiocyanate space.) The extracellular fluid normally comprises 18 to 24 per cent. of the body weight. In patients with œdema from starvation or other cause it may be increased to 50 per cent. of the body weight. In dehydration it is markedly reduced.

Details of laboratory procedures will not be given. An excellent laboratory manual has been provided by Consolazio *et al.* (1963).

Minerals

Of the 4·5 kg. of ash in the body about 4 kg. is in the skeleton and consists largely of calcium phosphate. It should be remembered that this amount is only about 45 per cent. of the weight of living bone, which also contains about 25 per cent. of water and 30 per cent. of organic matter.

The remaining minerals are distributed mainly in solution, as electrolytes in the soft tissues and fluids of the body. However, the distribution is not uniform ; the chief electrolytes are present in very different proportions in the intracellular and extracellular fluids. Throughout this book concentrations of electrolytes are given in milliequivalents (mEq.). Milliequivalents are converted into milligrams by multiplying by the sum of the atomic weights of the atoms composing the ion and dividing by the valency of the ion.

Table 1, 2 shows approximate concentrations of the most important ions. Potassium and phosphate predominate inside the cells and sodium and chloride in the fluids outside. Any table of ionic concentrations in the body may mislead by giving the impression that these remain static. The cell walls are permeable in varying degree to inorganic ions, which are continually passing in and out. The difference between the concentration of the ions within and without can only be maintained by the expenditure of energy, which is provided by the metabolic processes within the cells. Much of the energy expenditure of the resting body is used to maintain this electrolyte equilibrium. Cellular activity either in muscle, nerve or secretory cell is associated with local disturbances of ionic equilibrium at the cell wall and chemical energy is needed to restore resting conditions.

TABLE 1, 2. *A normal distribution of ions in intracellular and extracellular fluids*

	Intracellular (mEq./*l.*)	Extracellular (mEq./*l.*)
Cations :		
Na^+	10	145
K^+	150	5
Ca^{++}	2	2
Mg^{++}	15	2
	177	154
Anions :		
Cl^-	10	100
PO_4^{--}	90	2
HCO_3^-	10	27
SO_4^{--}	15	1
Organic acids	...	5
Proteins	52	19
	177	154

The lean body mass

This term is used to describe the first three chemical compartments listed on page 2, namely the cells, the extracellular fluid and the mineral skeleton. In living man of course, it can only be measured indirectly. Analyses of animal carcasses have shown that the total body water distributed through both cells and extracellular fluid is approximately 70 per cent. of the weight of the fat-free portion of the body, provided the animal is in normal health and water balance.

Total body water $\times \frac{100}{70}$ is thus an indirect measure of lean body mass.

Total body weight minus lean body mass gives the weight of body fat. The lean body mass calculated in this way includes the small amount of water and cellular material present along with the fat in adipose tissue.

In all branches of physiology and medicine corrections for body weight are frequently used in adjusting the requirements of an individual for food or drugs and in comparing an individual against accepted standards of normality. It is probable that for many purposes, especially in obese persons, the lean body mass provides a better reference than body weight. The lean body mass is a more accurate measure of the actively metabolising tissue.

An excellent account of the theoretical and practical difficulties in determining total body water and lean body mass, with results of measurements on thin, normal and obese people, is given in a paper by McCance and Widdowson (1951).

Body fat

An estimate of total body fat can be made by determining total body water, as already indicated. Other methods are available. Of these the most studied is the density method, based on the common observation that fat floats. A comprehensive review of this method is given by Keys and Brozek (1953).

Attempts to assess the fat content of man and animals from measurements of their density have been occasionally reported for many years. Interest was renewed as a result of a practical problem. Some men on a draft for recruitment into the United States Navy were marked unfit for service by a medical board because their weights exceeded the maximum permissible for their height. As these men were professional footballers in civil life, it seemed unlikely that they were unfit for naval service because of obesity. A U.S.A. naval surgeon, Behnke and his associates (1942), examined the men. They were weighed in air and under water. Their density was thus calculated and found in some cases to be as high as 1·090 to 1·097, indicating a very low proportion of fat, which has a density of 0·901. From this it was concluded that the excess weight was mainly due to extra muscle and not fat.

Under-water weighing has now been extensively studied. Once a suitable tank has been constructed the method is easy. As the water in the bath is around 37° C. the procedure is not unpleasant for the subject (as we can vouch from personal experience) and is applicable to active people of either sex. The main practical difficulty arises from the fact that the observed under-water weight has to be corrected for the upthrust of the air remaining in the subject's lungs. (The weighings are made at the end of a forced expiration.) The recorded under-water weight of the subject and the chair on which he sits is usually between 5 to 8 kg. The residual air in the lungs may vary in healthy individuals from less than 1 *l.* to more than 2 *l.* It usually increases with age. Employing a standard normal value for the residual air can introduce an error of 20 per cent. or more in the true under-water weight. If precision is required, it is essential to measure the residual air in the lungs of each individual at the time of the actual weighing. This is not a difficult procedure provided the equipment and the experience of a respiratory physiologist are available. However, it limits the use of the method in routine clinical investigations.

The real difficulty in calculating the total fat from the density measurement and body weight in air arises from the impossibility of getting a *direct* measure of the density of the lean body mass in man. Human fat has a density of 0·901 g./ml. with very little individual variation. Various figures around 1·1 g./ml. have been taken for the density of the lean body mass. These are based on measurement of the density of animal carcasses. Keys and Brozek have calculated that if a normal man of density 1·0629 is assumed to have a fat content of 14 per cent. (an eminently reasonable assumption) then the percentage of fat (F) in a person of density D is given by the equation

$$F=\frac{420}{D}-381.$$

Estimates of body fat in the same individual calculated from measurements of total body water and of density have been shown to agree very well. Either method could be used for purposes of clinical investigation, provided the necessary laboratory skill and equipment are available. Estimates of the weight of fat in a human body, accurate to about ±10 per cent., should be possible. Neither method can give a reliable estimate in a subject in whom there is a significant disturbance of the water content of the body, with dehydration on the one hand or œdema on the other.

NORMAL FAT CONTENT OF THE BODY.—Only one large series of determinations has been reported (Keys, 1955). The figures presented in Table 1, 3 were obtained by under-water weighings of apparently healthy, city-dwelling Americans in Minnesota. Whether or not these figures would be found in other populations is not known. Perhaps Minnesotans would enjoy better health and greater freedom from disease if they carried less fat about on themselves. This question is considered in Chapter 27.

TABLE 1, 3. *Mean values for density and body fat content of typical urban Americans*

Sex	Average age	Density	Per cent. weight as fat
Male . . .	25	1·063	14
Female . . .	24	1·041	25
Male . . .	55	1·039	26
Female . . .	56	1·016	38

THE CHEMICAL COMPOSITION OF INFANTS

At birth the water content of the body is high and, as measured by the deuterium or antipyrine space (Friis-Hansen *et al.*, 1951), may be as much as 80 per cent. of the body weight. Both for premature and normal infants the relation between body water and body weight calculated from the observed data was found to be :

$$\text{body water in litres} = 0{\cdot}55 \times \text{weight in kg.} + 0{\cdot}51.$$

The percentage water content of the body falls in the first weeks of life, and by 6 months the adult figure of about 60 per cent. is reached. Most of this excess water is present in the extracellular fluid ; the thiocyanate space represents on the average 40 per cent. of the body weight (and may be as high as 47 per cent.) in newborn infants (Barnet, 1956), as compared with 24 per cent. in the adult. The increase in extracellular fluid cannot account for all the extra water and the amount in the cells must also be higher than in the adult. The fat content of the newborn infant is low ; usually about 5 per cent. of the body weight. The serum of the newborn differs from that of the adult in containing a little less protein and bicarbonate, but more chloride and phosphate (McCance, 1950). The concentration of sodium is the same as in adults.

CHAPTER 2

ENERGY

SECTION 1: HISTORY

JUST before the French Revolution Lavoisier and the physicist Laplace carried out experiments in which they placed a guinea-pig in a very small closed chamber surrounded by ice. They measured the amount of ice melted over a 10-hour period and at the same time the amount of carbon dioxide given out by the animal. They demonstrated that there was a relationship between the heat produced by the animal and the respiratory exchange. Lavoisier also measured the oxygen consumption of men, and showed that it increased after food and exercise. A letter, reproduced in an appendix (p. 34), which he wrote to Dr Black, then Professor of Chemistry and Medicine at Edinburgh and the discoverer of carbon dioxide, shows the extent of his experiments.

Lavoisier has properly been considered the founder of the modern science of nutrition. For over a hundred years after his death on the guillotine, ingenious and learned men exercised their talents in designing calorimeters in which laboratory animals and men could live for many hours or even a few days whilst their metabolism was studied. In 1849 Reynault and Reiset in Paris carried out numerous experiments on small animals and planned to construct a human respiration chamber in a large hospital. They were unable to get the necessary funds and they had to drop their project. Pettenkofer and Voit were more fortunate. They acquired the patronage of King Maximilian II of Bavaria. By 1866 they had constructed at Munich a chamber in which a man could live for several days and have all his respiratory exchanges measured. After measurements on a fasting man lasting 24 hours, the protein ' burned ' was calculated from the urinary nitrogen and the fat from the respiratory carbon dioxide (after deducting the carbon in the protein burned and assuming no change in the carbohydrate store of the body). A difference of only 6·2 per cent. was found between the measured oxygen absorption and that calculated as necessary for the combustion of the body materials metabolised. This accuracy indicates both their experimental skill and the soundness of the assumptions on which their calculations were based.

Rubner in Berlin, Zuntz in Switzerland and Johansson in Sweden were others who from 1880 onwards extended the work of the Munich school and so laid many of the foundations of modern nutritional science. But it was the American, Atwater, a pupil of Voit in Munich, who carried out the experiments which have established the essential quantitative physiological knowledge on which all assessments of the energy needs of men are based. Atwater returned to the U.S.A. from Germany in 1892 and enlisted the help of Rosa, an engineer. Together they constructed a human calorimeter which could measure the heat produced by a man with an accuracy of 0·1 per cent. At the same time the chamber incorporated the respiration apparatus used by Pettenkofer and Voit. Table 2, 1 illustrates one of Atwater's experiments.

TABLE 2, 1. *An experiment of Atwater and Benedict* (1899)

	Total 4 days	Average 1 day
(*a*) Heat of combustion of food eaten	9848	2462
(*b*) Heat of combustion of fæces	304	76
(*c*) Heat of combustion of urine	538	135
(*m*) Heat of combustion of alcohol eliminated	84	21
(*d*) Estimated heat of combustion of protein gained (+) or lost (−)	−277	−69
(*e*) Estimated heat of combustion of fat gained (+) or lost (−)	−539	−135
(*f*) Estimated energy of material oxidised in the body $a-(b+c+m+d+e)$	9738	2434
(*g*) Heat determined	9576	2394
(*h*) Heat determined greater (+) or less (−) than estimated $(f-g)$	−162	−40
(*i*) Heat determined greater (+) or less (−) than estimated $(h+f)$ (per cent.)	...	−1·6

When in 1906 Sir Frederick Gowland Hopkins at Cambridge carried out his experiments which demonstrated beyond doubt the existence of ‘ accessory food factors ’ (later known as vitamins), Atwater had completed his work. A chapter had been written in the textbooks of physiology which has needed no subsequent revision. After Hopkins' discovery, interest shifted sharply from the energy needs to the vitamin needs of both man and animals. The quality rather than the quantity of an individual's food became the foremost interest.

In 1940 a swing-back began. The limited food supply of many of the people of Western Europe led to a practical interest in the quantities of food necessary for the individual and for populations. Starvation lurked round the corner and was no longer confined to distant Asia. At the same time there arose a new interest in the energy requirements for work in industrial urban communities. With the mechanisation of industry and improved transport facilities the proportion of the workers who regularly took hard physical exercise declined. The proportion of sedentary workers increased correspondingly. At the same time more and more people became spectators rather than participants in active sports. These tendencies which were first apparent at the beginning of this century have only recently been widely appreciated. They have necessitated a new appraisal of the food requirements of man.

Section 2 of this chapter is an account of the classical physiology of energy exchanges. It differs very little from accounts written in the early part of the century and it is extremely unlikely that any essential changes will be made in the future. Excellent accounts of the subject by writers personally associated with the classical experiments have been given by Graham Lusk (1906) and Magnus Levy (1907). All serious students of the science of nutrition should read carefully one or other of these books which describe in detail so much of the work that is fundamental to the science.

Section 3 attempts an appraisal of the food requirements of contemporary man. It is a guide for those responsible for food planning or for drawing up ration scales. In contrast to Section 2 much of it rests on a limited experimental and scientific basis. However, practical policies have often to be decided by judgments based on inadequate data.

SECTION 2: BASIC PHYSIOLOGY

The Forms of Energy

The biologist is interested in energy in five forms:

1. Solar.
2. Chemical.
3. Mechanical.
4. Thermal.
5. Electrical.*

In plants and animals the various forms of energy are quantitatively interchangeable. It has been frequently demonstrated that living creatures, like inanimate matter, can neither create nor destroy energy but can only transform it and so obey the first law of thermodynamics, which states the principle of the conservation of energy.

Animals differ from green plants in that they cannot utilise solar energy directly. Green plants are able to synthesise complicated organic substances such as carbohydrates, proteins and fats from simple inorganic materials, such as CO_2, H_2O, NH_3 and SO_4. In this process (photosynthesis) solar energy is used and converted into chemical energy which can be stored by the plant. Plants, which are independent of other forms of life, are thus distinguishable from all animals, which are wholly dependent on plants. This is true now. It may not be so in the future, if chemists succeed in making synthetic foods on an adequate scale.

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* The existence of powerful electric organs in some fish is a clear-cut demonstration that animals can generate electrical energy: most electrical organs in fish are modified muscle end-plates. The processes of excitation in both muscle and nerve are dependent on electrical changes on the cell membranes. At the cellular level, electrical energy becomes very important. Only very occasionally, as when the electric eel stings its prey, is electrical energy liberated by the body as a whole.

Animals get their energy from their food in a chemical form, which is derived directly or indirectly from plants. This energy is bound in molecules of carbohydrate, protein and fat. It can be liberated and utilised in the following ways :

1. In the performance of mechanical work.
2. In promoting the activity of the liver, brain and other organs.
3. In maintaining the body temperature.
4. In promoting growth by the synthesis of new chemical substances rich in energy.

The interconversion of the different forms of energy, and in particular the conversion of chemical energy into mechanical energy, is never an efficient process. Most of the energy is dissipated as heat. At best a man can convert 25 per cent. of the energy in his food into mechanical work. In this respect he is much more efficient than most steam engines and about on a par with a good internal combustion engine. Most of the energy obtained from food, coal and petrol is lost as heat and cannot be converted into useful work.

The heat developed when mechanical work is performed helps to maintain the temperature of the body. Unless the environmental temperature is very cold, even a small amount of muscular activity produces enough heat to maintain the temperature, especially if the heat is conserved by adequate clothing. Usually, therefore, the extra heat developed when hard mechanical work is done represents waste that must be eliminated if the temperature of the body is to be kept normal. This is effected by means of sweating, the extra heat being used up in the evaporation of the sweat.

Of the energy required for promoting the activity of the organs, a part is used in mechanical work within the body. The heart must have power to pump the blood round the circulation : energy is needed for the muscular effort of drawing air in and out of the lungs, and of moving the food along the alimentary canal, but particularly for maintaining the unstable equilibrium between the electrolytes in the intracellular and extracellular fluids as described in Chapter 1. This internal mechanical energy can only be derived from chemical energy set free by oxidative processes. Energy is also needed for the synthetic processes necessary to replace essential chemical substances lost in the body by wear and tear. The means by which energy is finally released within the individual cell is described in Chapter 9.

By convention nutritionists always express energy quantitatively in units of heat, the unit used being the large Calorie or kilocalorie, which may be abbreviated to Cal. or kcal. It is defined as the amount of heat required to raise the temperature of a litre of water from 15° to 16° C. It is written with a capital C (or with a small k in front) to distinguish it from the caloric unit used in physics written with a small c, which is 1000 times smaller.

THE ENERGY CONTENT OF FOODS

If a foodstuff is placed in a small chamber or bomb (Fig. 2, 1) and exposed to a high pressure of oxygen in the presence of a platinum catalyst, it can readily be ignited by a small electric current. All the organic material will be burnt and the heat liberated can be measured. The average heat of combustion of the three ‘ proximate principles ’—carbohydrates, proteins and fats—is shown in Table 2, 2. There are very slight differences in the heat of combustion of different proteins and fats. However, individual carbohydrates differ significantly. Rubner found values of 3·692 for glucose, 3·959 for sucrose and 4·116 for starch. In the animal body, the tissues are able to oxidise carbohydrate and fat completely to carbon dioxide and water, but the oxidation of protein is never complete. Nitrogenous substances derived from protein such as urea, uric acid and creatinine are excreted in the urine. Many observations of the heat of combustion of urine have shown that it contains unoxidised material equivalent to 7·9 Cal./g. of nitrogen or 1·25 Cal./g. of protein oxidised by the body. It is therefore necessary to subtract 1·25 Cal./g. from the heat of combustion of protein (5·65 Cal./g.). Further corrections are necessary to allow for the incomplete absorption of nutrients in the alimentary canal. Atwater, over fifty years ago, made a large number of experiments in which he analysed the fæces of three young American men for periods lasting for 3 to 8 days, whilst on mixed diets typical of the time. He concluded that 92 per cent. of protein, 95 per cent. of fat and 97 per cent. of carbohydrate was normally absorbed. From this the ‘ Atwater Factors ’ for the available energy of the three different proximate principles (as given in Table 2, 2) have been derived. It is important to remember that these factors make allowance for the calories in the food lost in fæces and urine. They are physiological approximations based on experiments on a limited number of subjects on one kind of diet. However, experiments by Dr Durnin and Dr Widdowson in Glasgow, which are as yet unpublished, show that these factors are probably widely applicable.

TABLE 2, 2. *The heat of combustion and the available energy in the three proximate principles in a mixed diet*

	Heat of combustion (Cal./g.)	Available energy (Cal./g.)
Carbohydrate . .	4·1	4·0
Protein . . .	5·65	4·0
Fat	9·4	9·0

In practice, the energy values of diets are calculated from tables of food analyses, of which many are available (Chapter 16). These tables give figures for the carbohydrate, protein and fat content of each food as determined by chemical analysis ; the caloric value of the food is calculated by multiplying these figures by the Atwater Factors or some variant of them. Differences may arise from the methods of calculating the results. The protein content of each food is always determined from its nitrogen content. Most proteins contain about 16 per cent. of nitrogen. To calculate the protein content of foods, the nitrogen content has frequently been multiplied by 6·25, but this figure is only an approximation and certainly too high for cereals and too low for milk. For these 5·7 and 6·4 per cent. respectively are better values, and have been used by some authors in the construction of their tables. As already stated the heat of combustion of the different carbohydrates varies significantly. In older tables of food analyses the carbohydrate content has often been calculated by difference, *i.e.* the carbohydrate content of the food is taken to be the difference between the total weight and the sum of the water, protein, fat and mineral content. In some modern tables the amount of glucose, fructose, sucrose, dextrins and starch in each food has been estimated separately and appropriate caloric values applied.

In general all these differences and inconsistencies are small in comparison with the variations between different samples of the same food. In particular almost all animal foods have a very varying fat content and this may greatly affect their caloric value. On the other hand the chemical composition of a given variety of a cereal is relatively constant.

Despite all these uncertainties the caloric values for foods given in tables of food composition are of practical use in the dietetic departments of hospitals and in public health departments. They are unlikely to lead to any serious error in making up diets for an individual patient or for prescribing ration scales for institutions, service personnel, etc. They are well tried and practical guides. The intelligent user would, however, be well advised to find out exactly how the caloric values in his particular table have been obtained and to keep an eye open for possible anomalies. An excellent account of the history of the various factors in use to-day with full references to the classical papers has been given by Widdowson (1955) and McCance and Widdowson (1960).

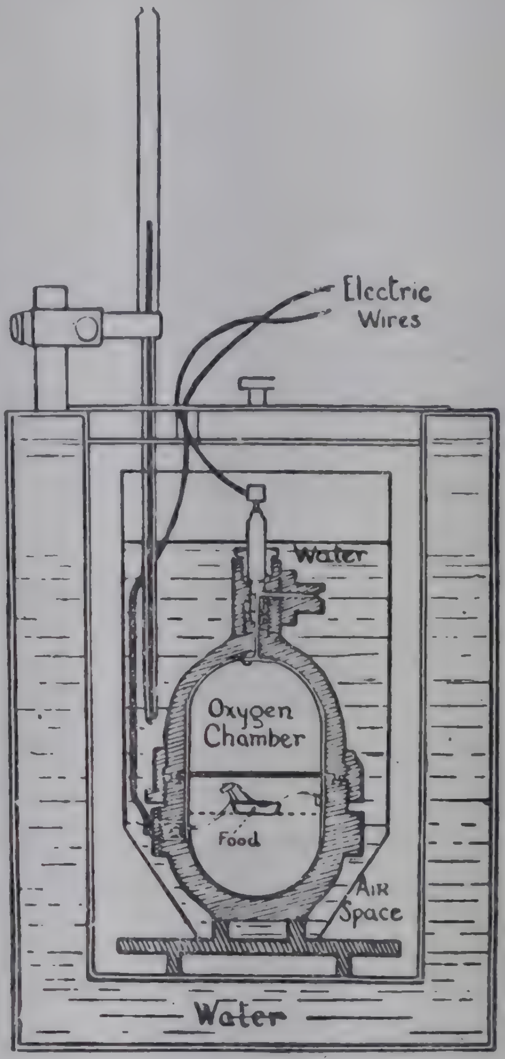

FIG. 2, 1. **The bomb calorimeter**

The bomb is placed inside a vessel of water, the temperature of which can be accurately measured. The foodstuff is placed in a small crucible. The bomb is filled with oxygen at high pressure and the foodstuff ignited by means of electric leads. The material in the bomb burns and the heat produced leads to a rise of temperature in the surrounding water.

The uncertainties inherent in all tables of caloric values of food make them of little use to the research worker, who wishes to feed diets of accurately known caloric content for metabolic balance studies on patients or laboratory animals. For such there is no escape from painstaking analyses of aliquot samples of the foods eaten and the urine and fæces excreted.

Alcohol can serve as a source of calories for man. The heat of combustion of ethyl alcohol is 7 Cal./g. and under favourable circumstances, as Atwater showed, all this energy can be utilised by man. How much of the alcohol ingested is actually used under different dietary circumstances is a difficult problem, which will be considered in Chapter 7.

Sheep and other ruminants are able to derive considerable amounts of energy from cellulose, which is broken down by bacteria in the alimentary tract to short-chain fatty acids : these are subsequently absorbed into the circulation and metabolised. There is no evidence, however, that man can ever derive a significant amount of energy from cellulose.

THE MEASUREMENT OF ENERGY EXPENDITURE

Direct Calorimetry is easy in theory, though difficult and costly in practice. If an animal or man is put into a small chamber in which all the heat evolved can be measured, then the total energy expenditure is the sum of that heat *plus* any mechanical work performed (as on a stationary bicycle). Fig. 2, 2 is a diagrammatic representation of the Atwater and Rosa chamber. With this they were able to demonstrate effectively that in man :

1. Total energy expenditure (the sum of the heat produced plus the mechanical work done) was equal to the net energy from the food consumed (the total chemical energy in the food *minus* the energy lost in the fæces and urine). They left no doubt that man obeys the fundamental physical law of the Conservation of Energy.
2. Total energy expenditure is quantitatively related to the oxygen consumption.

Indirect Calorimetry is the measurement of oxygen consumption. It is technically a far simpler procedure than the measurement of heat. In human physiology indirect calorimetry has for many years replaced direct calorimetry in the study of energy expenditure. Animal physiologists, however, use calorimeter chambers and in Scotland there are two, one for sheep at the Rowett Research Institute and one for cows and calves at the Hannah Dairy Research Institute.

A carbohydrate such as glucose and a typical fat such as tripalmitin are oxidised completely according to the following equations :—

$$C_6H_{12}O_6+6\ O_2=6\ CO_2+6\ H_2O$$

$$2\ C_{51}H_{98}O_6+145\ O_2=102\ CO_2+98\ H_2O.$$

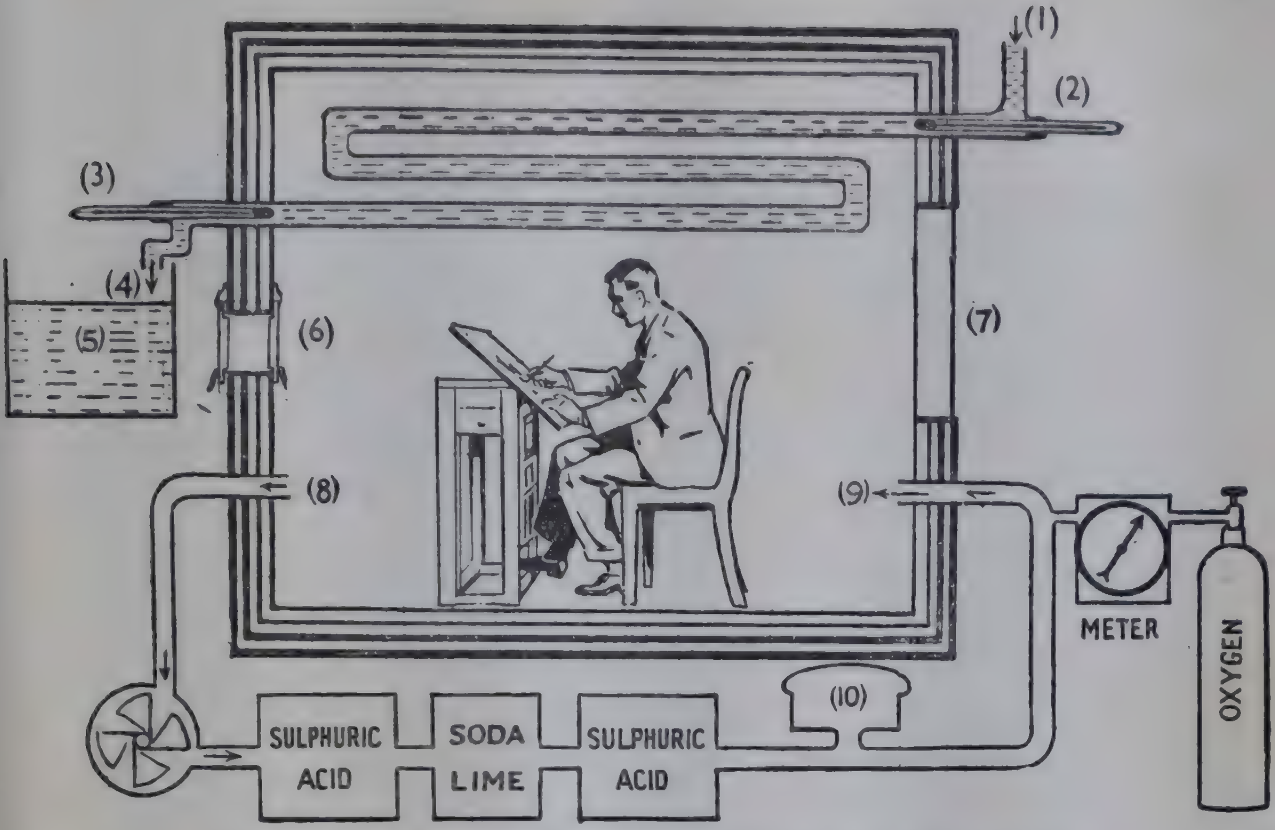

FIG. 2, 2. **The Atwater Benedict respiration calorimeter**

The walls of this chamber are insulated. Heat produced in it is absorbed by water passing in at (1) and out at (4), its temperature on entering and leaving being recorded on the thermometers (2) and (3). The volume of water that has flowed through the cooling system is measured in the vessel (5). The subject may be observed through the window (7), while food may be introduced and excreta removed through the porthole (6). Air leaves the chamber at (8) and passes through a blower and over sulphuric acid and soda-lime to absorb water and carbon dioxide. Oxygen measured by a gas meter is added to the system before the air passes into the chamber at (9). (10) is a tension equaliser. (From BELL, G. H., DAVIDSON, J. N. & SCARBOROUGH, H. (1961). *Textbook of Physiology and Biochemistry*. Edinburgh : Livingstone.)

One gram molecular weight of glucose requires 6 g. molecular weights of oxygen and the carbon in it yields 6 g. molecular weights of carbon dioxide. But 1 g. molecular weight of a gas occupies 22·4 *l.* (Avogadro's Law). Hence 180 g. of glucose utilise $6 \times 22{\cdot}4$ *l.* of oxygen and yield $6 \times 22{\cdot}4$ *l.* of CO_2. One litre of oxygen used for the combustion of glucose only will thus be responsible for $\frac{180}{6 \times 22{\cdot}4} = 1{\cdot}34$ g. of carbohydrate. But 1 g. of glucose has a heat of combustion of 3·692 Cal./g. (Rubner). Hence 1 *l.* of oxygen when oxidising glucose will liberate $1{\cdot}34 \times 3{\cdot}692 = 4{\cdot}95$ Cal.

It will be seen that for glucose the ratio of the volumes of $\frac{\text{carbon dioxide produced}}{\text{oxygen utilised}} = 1$. This ratio is known as the *Respiratory Quotient* (R.Q.). For the oxidation of the fat in the above equation the R.Q. $= \frac{102}{145} = 0{\cdot}703$. There is thus a big difference in the R.Q. of fat and carbohydrate. This fact enables the R.Q. to be used as a measure of the proportion of fat to carbohydrate being oxidised. Zuntz developed a method for calculating the energy yields for each of the proximate principles from measurements of respiratory exchange. His results are summarised in Table 2, 3. From these data he drew up another table giving the caloric values of 1 *l.* of oxygen at different values of the R.Q. and the proportion of the heat provided by fat and carbohydrate. Zuntz's original table has been slightly modified by later workers, who have obtained more accurate figures for the heat of combustion. Table 2, 4 gives a modification of Zuntz's table.

In experiments in a respiration chamber lasting 24 hours or more it is possible to calculate from the measurement of the urinary nitrogen the energy derived from protein and the oxygen utilised in the process. The Cathcart-Cuthbertson table can then be applied to the non-protein respiratory exchange. However, measurements of oxygen uptake are usually made over periods of 5 to 10 min. During such a time the amount of energy provided by protein is very small, usually 12 to 14 per cent. of the total. Protein has an R.Q. midway between that of fat and carbohydrate and an energy equivalent for oxygen very similar to that of fat. Hence only a trivial error is introduced by neglecting protein and applying the Cathcart-Cuthbertson table to the figure obtained by measurement of the oxygen utilisation and the total R.Q.

TABLE 2, 3. *Energy yields from oxidation of foodstuffs* (Zuntz, 1897)

1 g. of—	O_2 required	CO_2 produced	R.Q.	Cal. developed	Cal. equivalent of 1 *l.* of O_2
	ml.	ml.			
Starch . . .	828·8	828·8	1·000	4·183	5·047
Animal fat . .	2019·2	1427·3	0·707	9·461	4·686
Protein . . .	966·1	781·7	0·809	4·442	4·600

TABLE 2, 4. *Caloric value of oxygen* (Cathcart & Cuthbertson, 1931)

Non-protein R.Q. (see text)	Cal. per litre of O_2	Per cent. total Cal. from	
		Carbohydrate	Fat
0·72	4·735	0·0	100·0
0·75	4·770	12·0	88·0
0·80	4·827	30·4	69·6
0·85	4·881	48·4	51·6
0·90	4·936	66·0	34·0
0·95	4·992	83·2	16·8
1·00	5·047	100·0	0·0

The data in Tables 2, 3 and 2, 4 all depend on accurate figures for the heat of combustion of carbohydrate, fat and protein as actually utilised by the body. There are minor differences in the chemical constitution (and also probably of the heat of combustion) of the foods oxidised by different species and also perhaps by individuals of the same species. For this reason the accuracy of the data probably does not really justify the giving of the figures to three places of decimals, as is used in these tables. Nevertheless errors arising from this source are trivial. There is no doubt that these tables enable total energy expenditure to be determined by indirect calorimetry with an error of less than 2 per cent.

The measurement of oxygen consumption.—The oxygen consumption of man has been measured in respiration chambers, where there is the advantage of being able to record it over long periods.

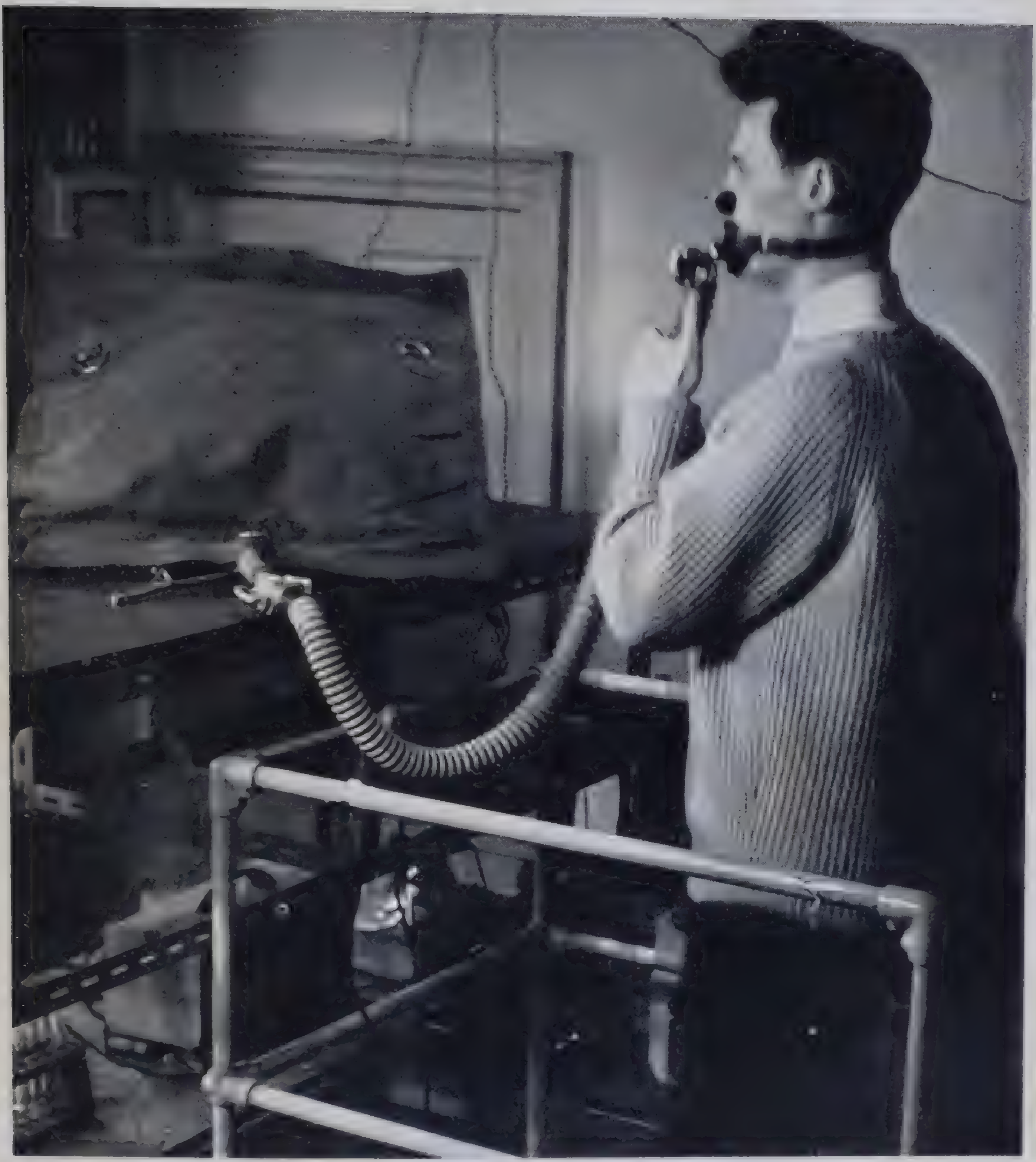

Plate I. **A Douglas bag**

The subject, who is walking on a treadmill, is breathing in room air through an inspiratory valve and breathing out through an expiratory valve into a Douglas bag. The two valves are housed in the mouthpiece. The air collected in the Douglas bag can be measured subsequently and its content of CO_2 and O_2 analysed. A Douglas bag is the most reliable method for indirect calorimetry in the laboratory.

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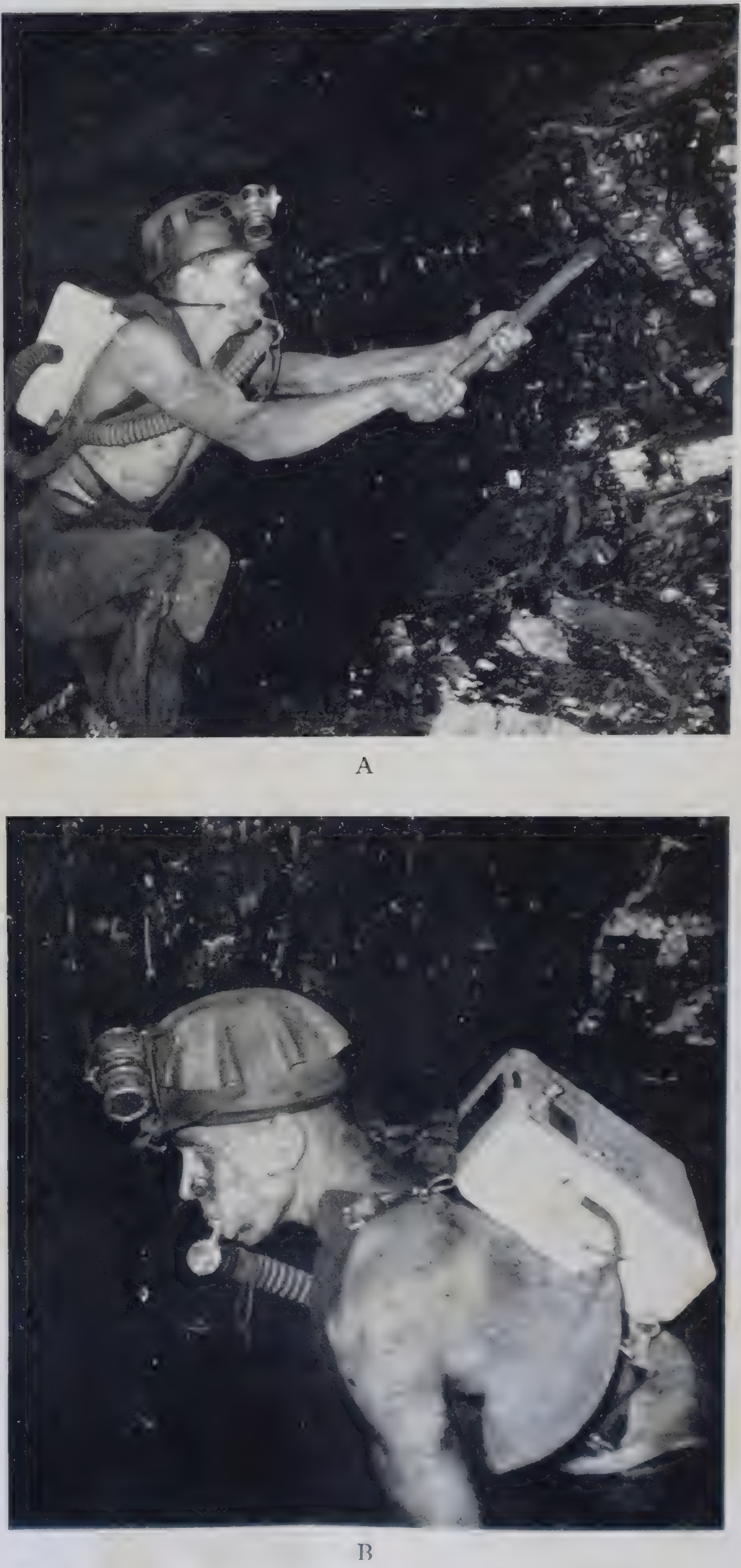

PLATE II. **The Kofranyi-Michaelis respirometer in action**

A, A miner hewing coal. B, shows the collecting bag. The Kofranyi-Michaelis respirometer is more convenient to use than the Douglas bag and has replaced it for indirect calorimetry under industrial conditions.

However, respiration chambers are expensive and difficult to manipulate (though far less so than calorimeter chambers) and, when within one, the subject's activities are necessarily limited. For these reasons most measurements of oxygen uptake are made when the subject is breathing into some form of apparatus, which can measure the total volume of gas expired (the ventilation rate) and provide a sample of expired air for analysis. This involves the use of valves which separate the inspired air from the expired air. These valves may be housed in a small metal or plastic box with a rubber mouthpiece which the subject grips between his teeth. Alternatively they may be housed in a rubber mask covering the face. Occasionally, a glass or plastic helmet which encloses the whole head and neck has been used. The rubber mouthpiece is most frequently employed. Some people experience an initial difficulty in breathing through valves and require a period of practice or ' training ' before reliable results are obtained. Indeed all subjects need a few minutes' practice before they will breathe naturally through a strange apparatus. For most people such a short period is all that is necessary and, in our experience, the importance of prolonged training has often been exaggerated.

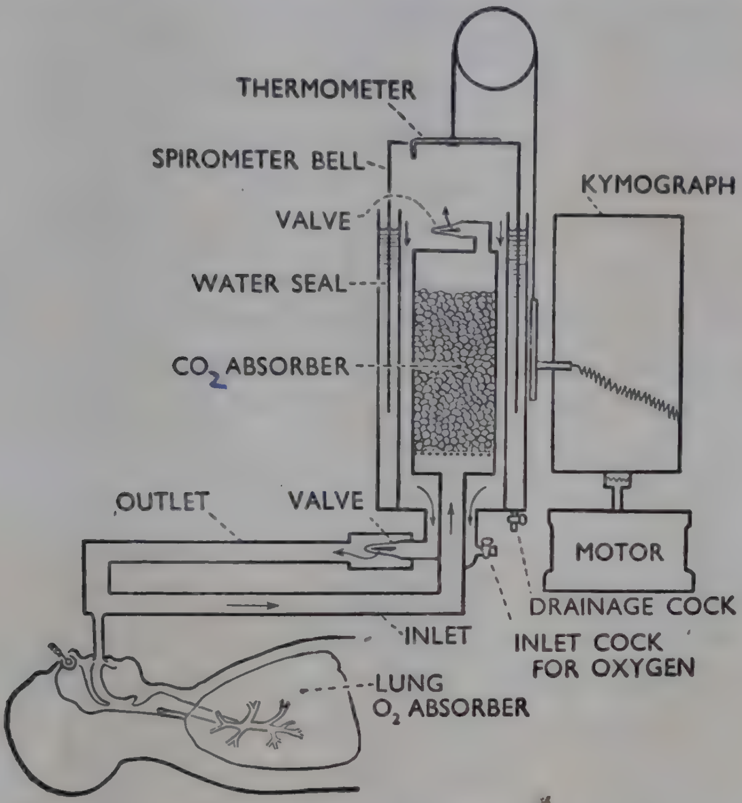

FIG. 2, 3. **Benedict Roth spirometer**

The subject wears a nose-clip and breathes through a mouthpiece which is connected to the apparatus by two valves. He breathes in oxygen through the inspiratory valve and breathes out through the expiratory valve into the carbon dioxide absorber. The amount of oxygen used is recorded on the revolving drum by the pen attached to the counter weight. (Diagram by J. B. de V. Weir.)

Many different types of apparatus have been designed and several are in general use to-day. The *Benedict Roth spirometer* (Fig. 2, 3) is a closed circuit system in which the subject breathes in oxygen from a metal cylinder about 6 *l.* in capacity, and the expired air passes back through a soda-lime canister (to absorb the carbon dioxide) into the same cylinder. The cylinder floats on water inside a second cylinder. As the oxygen is consumed the inner cylinder falls and the rate of fall is recorded by an ink-writer on a rotating drum. The Benedict Roth apparatus is widely used in hospitals for measuring the resting or basal metabolism, for which purpose it is eminently suitable. It is very simple to use and the direct reading of oxygen consumption avoids the necessity of gas analyses. As the carbon dioxide is not measured the R.Q. cannot be calculated and the heat equivalent of oxygen is always assumed to be 4·8 Cal./*l.* As the apparatus is not portable it can only be used when the subject is at rest either lying or sitting. The physiologist is usually interested in the carbon dioxide production as well as the oxygen consumption. To measure both, the subject after breathing in ordinary room air breathes out into a *Douglas bag* (Plate I), which is made of rubber and usually of 100 *l.* capacity. The expired air is collected for a period of 3 to 10 minutes. The air in the bag is then passed through a gas meter, measured and a portion set aside for subsequent analysis of the carbon dioxide and oxygen content. The Douglas bag method is the simplest and most reliable means of measuring the respiratory exchanges. It is the method of choice in the laboratory. However, it is cumbersome and clumsy to use for experiments in the field or in industry. For measurements of energy expenditure during industrial work and everyday life, the procedure has been greatly facilitated by the development in Germany of the *Max Planck respirometer* (Müller & Franz, 1952). This apparatus (Plate II and Fig. 2, 4) is a light-weight portable respirometer, which can measure directly the volume of the expired air and simultaneously divert a small fraction into a football bladder for subsequent analysis. The instrument weighs only about 5 lb. and can be worn on the back like a haversack. Its introduction has made possible the systematic measurement of the energy used in a variety of normal occupations as diverse as housework and coalmining.

Another respirometer, called the Integrating Motor Pneumotachygraph or IMP, has been designed by Wolff (1958). In as much as it has a very low resistance and is accurate at high ventilation rates, it is a better instrument than the German one. However, it is more expensive and its reliability under field conditions has not been tested to the same extent as the Max Planck respirometer which has been well proven in many industries.

RATES OF ENERGY EXPENDITURE

Many thousands of measurements of the energy expenditure of men and women undertaking a great variety of activities have been made by indirect calorimetry. Passmore and Durnin (1955) have collected some of these data together into a series of tables, which provide estimates of

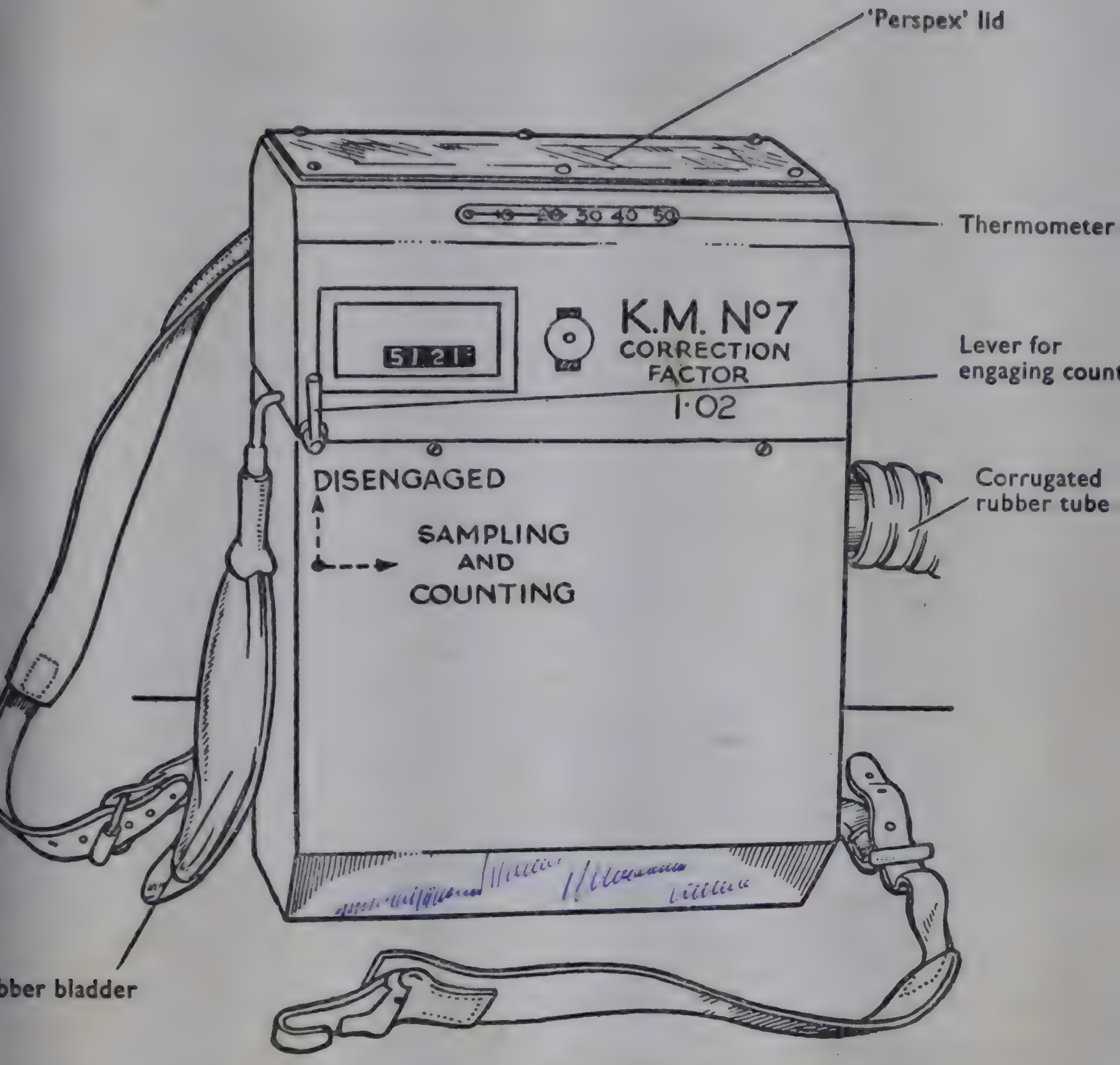

FIG. 2, 4. **The Max Planck respirometer**

The subject breathes out through an expiratory valve and the volume is directly measured and recorded on the counter. A portion of the expired air is diverted into the bladder (see Plate 2, B) for subsequent analysis. (From GARRY *et al.*, 1955.)

the energy output of man during his various activities in day-to-day life. These are in some ways complementary to the well-known food tables which provide estimates of the dietary energy intake. Table 2, 5 is a selection of figures given by Passmore and Durnin. These figures are expressed in Cal./min. and are measurements of energy expenditure when actually employed in each particular physical activity. To express results in Cal./hr., as has often been done, is less satisfactory since few people undertake the same physical activity consistently and continuously for an hour at a time.

There are naturally variations in individual efficiency in carrying out the same task, and these will affect the energy expenditure. The major part of human work consists in moving the body about and in most activities energy expenditure is closely related to body weight.

TABLE 2, 5. *Energy output during various activities determined by direct measurements of oxygen consumption in individual subjects*

	Age (years)	Weight (kg.)	Activity	Cal./min.
In bed	...	...	Sleeping or almost asleep	0·7–1·2
Recreations				
Woman	44	65	Sitting listening to music	1·2
Man	28	65	Sitting at ease	1·4
Girl	12	33	Drawing	1·5
Man	23	69	Writing a letter	1·9
Man	21	80	Listening to radio	2·0
Man	21	76	Playing canasta	2·1
Man	...	62	Playing violin	2·7
Man	32	70	Playing bowls	4·4
Man	21	80	Dancing foxtrot	5·2
Man	32	67	Cycling	6·6
Man	23	69	Dancing eightsome reel	7·5
Man	21	77	Swimming, breast stroke	9·6
Man	...	...	Ski-ing, light skis	14·5
Woman	...	68	Ski-ing, hard snow, uphill maximum speed	17·9
At work				
1. *Domestic work*				
Woman	22	50	Dishwashing	1·4
Woman	22	50	Washing towels	1·8
Woman	43	84	Cooking	2·4
Woman	44	65	Mopping	3·5
Man	46	65	Cleaning windows	4·0
Woman	44	65	Scrubbing floor	5·2
Woman	55	80	Putting washing through mangle	6·0
Man	21	76	Bedmaking	7·6
2. *Clerical work* (sedentary work)				
Range of 36 observations on 10 men			Miscellaneous office work	1·2–1·9
3. *Light engineering* (light work)				
Average of 3 women			Machine sewing	4·5
Average of 12 men			Machine fitting	4·2
Average of 9 men			Plastic moulding	3·3
Average of 18 women			Ebonite and plastic finishing	2·4
4. *Coalmining* (heavy work)				
Range for 18 men			Hewing	5·0–10·5
Range for 20 men			Loading	6·0–8·9
Range for 18 men			Timbering	4·1–9·0
5. *Lumber work* (very heavy work)				
Range for 11 men			Tree felling	8·4–12·7
Range for 11 men			Cross-sawing	7·5–10·5

There have been many differences of opinion as to what constitutes hard work. A physiological definition would be useful; Table 2, 6 presents quantitative definitions of work intensities. It is based on a study by Christensen (1953) in the Swedish iron industry, but is generally applicable. The figures given are for men of about 65 kg. Resting and walking are common to all healthy men and women and together make up a large proportion of the total daily energy expenditure. Each will now be considered in more detail.

9.5 / 57.60

TABLE 2, 6. *Energy expenditure in relation to intensity of muscular work.* (After Christensen)

Grade of work		Cal./min.
Very light	less than	2·5
Light		2·5–4·9
Moderate		5·0–7·4
Heavy		7·5–9·9
Very heavy		10·0–12·5
Exceedingly heavy	over	12·5

Energy expenditure at rest

When a subject is at complete rest and no physical work is being carried out, energy is required for the activity of the internal organs and to maintain the body temperature, as already discussed. This energy is called the basal metabolism. The *basal metabolic rate* (BMR) is determined experimentally when the subject is lying down at complete physical and mental rest, wearing light clothing in a room comfortably warm and at least 12 hours after the last meal. A knowledge of the BMR is useful in a study of some diseases, notably in disorders of the thyroid gland. Excess thyroid gland activity greatly increases metabolism under basal conditions. Table 2, 7 gives standard values for the BMR of people of both sexes and of all ages. It is based on a compilation of many hundreds of observations on people in many countries. It will be observed that the results are expressed in Cal./sq.m./hr. Surface area has long been used to standardise measurements of the BMR in individuals of varying size. Rubner showed many years ago that animals so diverse as the horse, man, the dog and the mouse had very different BMRs if expressed in Cal./kg. of body weight, but the figures for each species are remarkably similar if expressed in Cal./sq. m. of surface area. The surface

TABLE 2, 7. *Standards for basal metabolic rates* (Fleisch, 1951) (*Cal./sq.m./hr.*)

Age (years)	1	3	5	7	9	11	13	15	17	19	20
Male	53·0	51·3	49·3	47·3	45·2	43·0	42·3	41·8	40·8	39·2	38·6
Female	53·0	51·2	48·4	45·4	42·8	42·0	40·3	37·9	36·3	35·5	35·3

Age (years)	25	30	35	40	45	50	55	60	65	70	75	80
Male	37·5	36·8	36·5	36·3	36·2	35·8	35·4	34·9	34·4	33·8	33·2	33·0
Female	35·2	35·1	35·0	34·9	34·5	33·9	33·3	32·7	32·2	31·7	31·3	30·9

area of a few men and women has been accurately determined by pasting small pieces of paper all over the body and measuring the area of the paper. From these measurements it was shown that surface area can be predicted from measurements of height and weight. The nomogram shown in Fig. 2, 5 has been constructed for this purpose and is in wide use.

While there is no doubt that surface area provides a convenient standard for comparing the BMR of different species, it is doubtful whether it is the best standard for assessing the BMR of individual members of the same species. In particular, in people whose body shape and composition depart markedly from the normal, the use of the surface area may mislead. This is certainly so in obese people. Several observers have now shown that the BMR is more closely related to the 'lean body mass' than to the surface area. When the figures are expressed in relation to the lean body mass the differences between men and women recorded in Table 2, 7 disappear. They are not the result of any fundamental differences in the metabolism of the two sexes, but simply reflect the fact that women are usually fatter than men (p. 6). Nevertheless, as the surface area can be assessed much more easily than the lean body mass it will probably continue to be used as a reference standard in routine work in hospitals. For research purposes, as in the study of obesity, it is a reference standard of limited value.

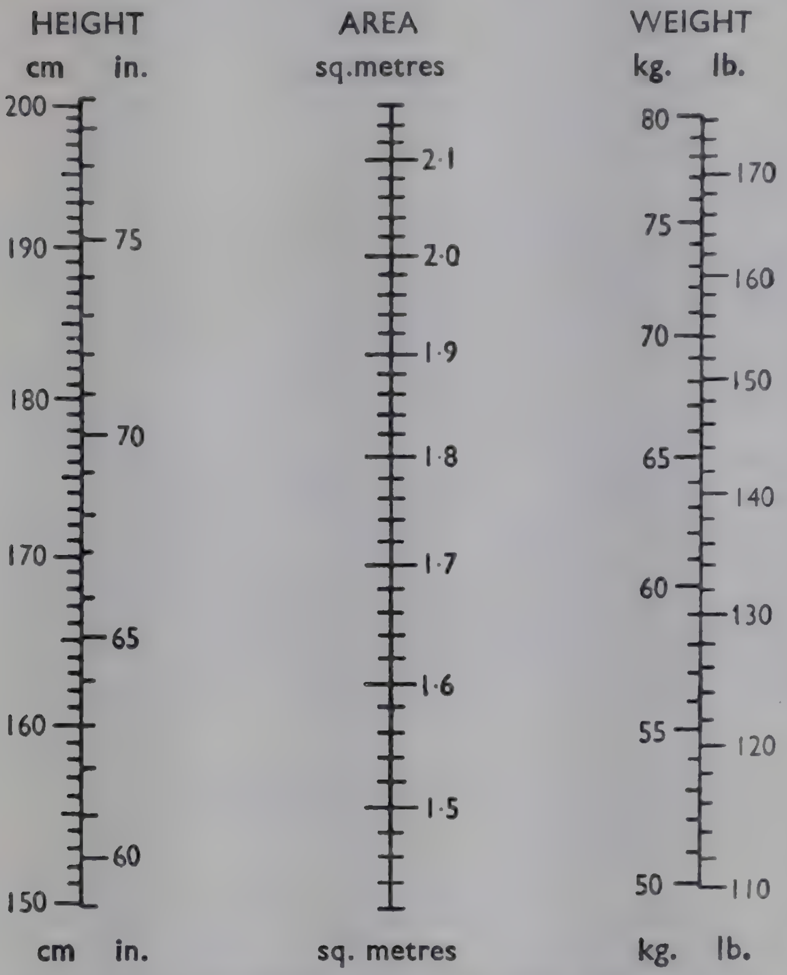

FIG. 2, 5. **Nomogram for calculating surface area**

A line joining the height on the left-hand scale to the nude weight on the right-hand scale cuts the centre scale at the predicted surface area. (From BELL, G. H. (1947). *Experimental Physiology*. Glasgow: Smith & Son.)

As Table 2, 7 shows, the BMR is high in actively growing young children and falls rapidly in the first 12 years of life. Thereafter a steady slow decline sets in.

In the tropics the natives usually have a BMR about 10 per cent. below the standards in Table 2, 7. Most (but not all) immigrants to the tropics from Europe and North America show a similar fall. The low BMR of tropical races is most likely an adaptation to the environment. There is no convincing evidence that there are any racial differences in the BMR.

Food has an important effect on energy expenditure and when taken by an individual at rest there is an increase in the production of heat. This effect is known as the *specific dynamic action* (SDA) of food. The SDA is dependent on the nature of the food taken. Thus if a fasting man, kept at complete rest at a normal environmental temperature, is given protein in an amount which should meet the basal caloric expenditure, his output of energy may increase up to 30 per cent., whereas with a similar amount of carbohydrate, the increase may be less than 5 per cent. But the response varies greatly from one individual to another.

The cause of the SDA of food is not definitely known, but there seems to be a stimulation of the cells of the body to greater activity by certain constituents of the food after their absorption. In the case of protein, individual amino acids have been shown to exert a SDA of varying intensity.

The heat produced by the SDA of protein contributes to maintaining the body temperature. This is a matter of importance to inhabitants of cold regions such as Eskimos who often obtain a very high protein intake from walrus meat. Conversely, it has been argued that in very hot climates the protein intake should be limited, but the importance of this effect of protein has been over-emphasised, since the extra heat which is produced is only a very small fraction of that resulting from muscular work. In practice, a high protein diet has no deleterious effect on the capacity for work at high temperatures ; it is therefore unnecessary to restrict the protein intake in hot climates.

When changing from the lying to the sitting or standing position the metabolism may rise by about 20 and 30 per cent. respectively. When sitting quietly in a chair throughout the day, metabolism can be taken to be about 20 per cent. above the basal rate *plus* an additional allowance of 10 per cent. for the SDA of food.

When asleep throughout the night, the overall metabolic rate approximates very closely to the BMR. When sleep begins, the SDA of the last meal may raise the metabolism slightly, but in the small hours of the morning it is usually a little lower than basal rates. This is probably due to a slight fall in body temperature. These two effects cancel each other and errors introduced in calculating total metabolism throughout the night from the BMR are negligible.

Energy expenditure when walking

This has been extensively studied in many countries. There can be no doubt about the complexity of the factors that may determine energy expenditure, but speed and body weight are the most important. Table 2, 8 gives figures for energy expenditure for people of different weights walking on the level at varying speeds. The table can be used as a guide to the amount of physical exercise needed to achieve a given expenditure of energy, when exercise is used as a means of weight reduction. The figures are unlikely to be in error by more than ±15 per cent. for any individual. They will not be applicable to anyone who is lame and so walks at a mechanical disadvantage.

TABLE 2, 8. *Energy expenditure* (*Cal./min.*) *related to speed of walking* (*m.p.h.*) *and gross body weight* (*lb.*). (Passmore & Durnin, 1955)

Speed (m.p.h.)	Weight (lb.)						
	80	100	120	140	160	180	200
	Cal./min.						
2·0	1·9	2·2	2·6	2·9	3·2	3·5	3·8
2·5	2·3	2·7	3·1	3·5	3·8	4·2	4·5
3·0	2·7	3·1	3·6	4·0	4·4	4·8	5·3
3·5	3·1	3·6	4·2	4·6	5·0	5·4	6·1
4·0	3·5	4·1	4·7	5·2	5·8	6·4	7·0

SECTION 3: THE CALORIC REQUIREMENTS OF MAN

When in health and with food freely available, each individual assesses his own caloric requirements with remarkable precision by means of his appetite. The mechanism of appetite is discussed in the next chapter. In clinical practice the assessment of a patient's caloric requirements usually requires a simple experiment which presents no difficulty. For instance, to find out whether 2500 Cal./day will provide sufficient energy for an accountant with diabetes to carry out his business in the office and pursue his usual recreations, all that is necessary is to give him a diet providing 2500 Cal. and observe if he gains or loses weight. There are wide variations in the caloric requirements of individuals, even of those following the same occupation and apparently leading similar kinds of lives. If exact knowledge of an individual's requirements is needed, resort to this simple experiment is necessary.

For large groups of people such as the armed forces of a country, members of expeditions, the inmates of prisons, orphanages, boarding schools and other institutions, some estimate of food requirement is essential. In time of scarcity, estimates of the caloric needs of a whole country are of great assistance in enabling food to be distributed equitably by rationing and other means. At all times, but especially when food is scarce, a government must have some estimate of the total caloric needs of the people in order to plan national agriculture and to regulate the import and export of food (Chapter 51). The assessment of caloric requirements is an old problem which presented itself even before Noah began to victual the Ark. It is ever-recurring.

Methods.—Voit in 1881 recorded the food consumed by labourers and artisans in Germany and concluded that the average labourer needs 3055 Cal./day. Similarly Atwater in 1902 calculated the caloric value of the diets of farmers in Connecticut and Vermont; he found that they consumed 3410 and 3635 Cal./day respectively. Since then **dietary surveys** have been carried out on a large scale in many countries. The information so obtained has been the basis of many estimates of human caloric requirements. The technique of dietary surveys is discussed in Chapter 50. The use of the data so obtained is subject to two inevitable drawbacks. (*a*) When food is available in abundance and there is nothing to restrict consumption, more food than is required may be eaten. On the other hand, when supplies are insufficient or purchasing power is low, consumption is likely to be less than optimal requirements. (*b*) The dietary survey can give no information of how the energy in the diet is expended; how much is needed for occupational activities and how much for off-work and recreational activities? With the changing patterns of life brought about by mechanisation in industry and increased means of mechanical transport, these are often important questions.

On the practical side, the carrying out of family dietary surveys (measuring all the food consumed over a period in one household) is relatively simple. They have been and are being carried out in many countries. Individual dietary surveys, in which all the food consumed by a single person is measured and which provide much more detailed information, are technically more difficult; a high degree of co-operation on the part of the subject is necessary. Though many individual dietary surveys have been carried out, in no country have they been performed systematically or on a large scale.

In recent years **surveys of energy expenditure** have been made in attempts to overcome the drawbacks inherent in the methods of dietary surveys. Such surveys demand the collection of two distinct types of data; (*a*) the recording, often minute by minute, of the diverse physical activities in which the subject spends his time, and (*b*) the assessment of the caloric cost of each activity either by direct measurement of oxygen consumption or from previously published tables. The sum of all the products (time spent in each activity multiplied by the caloric cost of that activity) equals the total energy expenditure. During the first world war surveys of this nature were carried out on workers in munition factories and in a few other industries. In Germany during the second world war a most thorough survey was carried out of the energy expenditure in all the major industries (Lehmann *et al.*, 1950). These surveys only recorded the energy expenditure at work. To assess dietary needs, an arbitrary figure for the caloric needs for non-occupational activities had to be added. In recent years research workers in Great Britain have shown that it is possible to measure non-occupational energy expenditure as well. Surveys covering the whole 24 hours for 7-day periods have been carried out on military cadets (Edholm *et al.*, 1955), colliery clerks and miners (Garry *et al.*, 1955), female shop assistants and their mothers (housewives) (Durnin *et al.*, 1957), elderly women living alone (Durnin *et al.*, 1961*a*) and elderly men in industry (Durnin *et al.*, 1961*b*). In all of these surveys the energy expenditure data have checked well with energy intake data from dietary surveys. The energy expenditure surveys have the advantage that they show the distribution of energy expenditure throughout the 24 hours (Table 2, 9).

TABLE 2, 9. *Average daily expenditure of energy (Cal.) by ten clerks (average age 28·3 years, weight 64·6 kg.) and by nineteen miners (average age 33·6 years, weight 65·7 kg.) as measured over a whole week by Garry* et al. (1955)

	Clerks	Miners
Asleep and day-time dozing	500	490
Activities at work	890	1750
Non-occupational activities and recreations .	1410	1420
Total .	2800	3660

Experience of energy surveys is as yet limited. However, it can be said that they are at least as accurate as dietary surveys. While it must be admitted that they are not easy to carry out and require a large staff, they are probably no more difficult than individual dietary surveys and in some circumstances may be much easier. Energy expenditure surveys are being increasingly used to supplement the information provided by dietary surveys in the assessment of caloric needs.

RECOMMENDED STANDARDS

Various tables indicating the caloric needs of man have been drawn up. Well-known examples are the Recommended Dietary Allowances of the U.S.A. National Research Council issued in 1944 and 1953 and the Report of the British Medical Association's Committee on Nutrition issued in 1950. The Food and Agriculture Organisation of the United Nations (1957*a*) have also issued a report on Calorie Requirements, a revised edition of a 1950 report. One of us (R. P.) was a member of the committee which was responsible for the 1957 report ; the following account follows this report very closely, sometimes *verbatim*.

It is important to remember that the recommendations in all tables apply only to large groups of people. Individual requirements may depart markedly from the figures given. The recommendations are intended to provide a measure of the food sufficient to supply the energy required for a fully productive working life and for active recreations. Scales of temporary and emergency rations to tide a population through a crisis are given in Chapter 53.

THE REFERENCE MAN AND WOMAN

The energy requirements of individuals are dependent on four variables :

1. Physical activity.
2. Body size and composition.
3. Age.
4. Climate and environment.

There are also extra needs for growth in childhood and adolescence and for pregnancy and lactation. The FAO Committee gave examples of a ' Reference Man ' and ' Reference Woman,' for whom these variables were defined in quantitative terms (Tables 2, 10 and 2, 11). The effect of each on caloric requirements can be considered separately.

TABLE 2, 10. *The energy expenditure of a ' Reference Man '*
(Weight, 65 kg. Age, 25 years. Mean annual environmental temperature, 10° C.)

				Cal./day
A.	8 hrs.	**Working activities :** mostly standing (overall rate, 2·5 Cal./min.)		1200
B.	8 hrs.	**Non-occupational activities :**	Cal./day	
		1 hr. washing, dressing, etc., at 3 Cal./min.	180	
		1½ hrs. walking at about 6 km./hr. at 5·3 Cal./min. . . .	480	
		4 hrs. sitting activities at 1·54 Cal./min.	370	
		1½ hrs. active recreations and/or domestic work at 5·2 Cal./min.	470	1500
C.	8 hrs.	**Rest in bed** at basal metabolic rate . .		500
		Total .		3200

FACTORS INFLUENCING ENERGY EXPENDITURE

Activity.—The degree of physical activity is the most important variable and at the same time the most difficult to assess in any population. The assumption is made that in most countries the mean activity of the adult population as a whole approximates to that ascribed to the Reference Man and Woman. In all countries some people will be much more

TABLE 2, 11. *The energy expenditure of a 'Reference Woman'*

(Weight, 55 kg. Age, 25 years. Mean annual environmental temperature, 10° C.)

				Cal./day
A.	8 hrs.	**Working activities** in the home or in industry: mostly standing (overall rate, 1·83 Cal./min.)		880
B.	8 hrs.	**Non-occupational activities:**	Cal./day	
		1 hr. washing, dressing, etc., at 2·5 Cal./min.	150	
		1 hr. walking at about 5 km./hr. at 3·6 Cal./min.	220	
		5 hrs. sitting activities at 1·41 Cal./min.	420	
		1 hr. active recreation and/or heavier domestic work at 3·5 Cal./min.	210	
				1000
C.	8 hrs.	**Rest in bed** at basal metabolic rate		420
		Total		2300

active, but others (perhaps more numerous) will be less active than the examples given in Tables 2, 10 and 2, 11. The figures strike a balance between the requirements of the sedentary and active groups. They are also averages intended to cover variations not only throughout the week but also throughout the entire year. In most countries the range of activity throughout the population is such that extremes tend to cancel each other out. In any large population the proportion of people whose occupation or way of life calls for a caloric intake in excess of 4000 Cal./day will be very small. Many occupations, in particular forestry and agriculture, may involve higher rates for long periods, but are brought below this figure by the seasonal nature of the work. Coalmining is the heaviest work in which large numbers of people are employed and it is independent of the seasons. In no country have surveys shown that miners expend more than 4000 Cal./day. Some sports and recreations demand a very heavy expenditure of energy, but these are seldom pursued uniformly throughout the year. At the other extreme the number of truly 'sedentary' people is very rare. A range of daily energy expenditure between 2400 and 4000 Cal./day for men and between 1700 and 2900 Cal./day for women would include the vast majority of healthy and active men and women. This range is ±800 Cal. and ±600 Cal. of the figures given for the Reference Man and Woman.

In highly industrialised countries such as the U.S.A. and Great Britain the increasing mechanisation of industry results in reduced energy expenditure at work, while at the same time facilities and opportunities for active physical recreations are increasing. The distribution of daily energy between occupations and recreations is thus constantly changing. There are no data providing quantitative figures for these changes, but our impression is that the decline in occupational energy is proceeding faster than the increase in recreational energy. If this is so, then the figures given for the caloric needs of the Reference Man and Woman may well overestimate their overall requirement in the future.

A figure for the mean energy expenditure of the adult men and women of any country can never be more than an intelligent guess and can only be supported by observations and measurements of a small sample of the population. However, for a particular category of people a properly selected sample can be surveyed with results which allow much more accurate assessments. This is being carried out in the Armed Services of Great Britain and the U.S.A. Service rations can be accurately adjusted to the activities of the troops. Practical assessments of the caloric needs of residents in schools, colleges, prisons, mental hospitals, convalescent homes, etc., present no great difficulty. Energy expenditure surveys are perhaps more likely to give an accurate picture of real needs than dietary surveys.

Body size and weight.—As already mentioned a large part of the mechanical work performed by man consists in moving the body about. Basal metabolism is also closely related to body weight. The FAO report discusses at length the relation between body size and energy expenditure. The conclusion reached is that caloric needs (E) and body weight (W) can be related by the expression $E = aW^{0 \cdot 73}$ where a has a constant value, 152 for men and 123·4 for women. The use of this complicated equation is supported by custom rather than scientific logic. An appendix to the report points out that the simple linear equations :

$$\text{For men}: \ E = 815 + 36 \cdot 6 \ W$$
$$\text{For women}: \ E = 580 + 31 \cdot 1 \ W$$

give values for E that do not differ from these obtained by using the first equation by more than 10 Cal. over the range 50 to 80 kg. for men and 40 to 70 kg. for women. Arithmetical calculations will be facilitated if the simple linear equations are used to determine the caloric needs of populations whose mean weights differ significantly from the 65 kg. and 55 kg. ascribed to the Reference Man and Woman. The equations also indicate that a large proportion (approximately three-quarters) of human energy expenditure is directly proportional to body weight and that a smaller proportion (approximately one-quarter) is independent of body weight. There is physiological evidence consistent with this generalisation.

In individuals whose body composition departs markedly from normal, these corrections should not be applied. For instance, while many moderately obese people carry around their load of extra fat with ease and efficiency, very obese people with 40 kg. or more of fat bear their burden with difficulty ; in such circumstances the muscles of the limbs, the heart and the diaphragm work at a mechanical disadvantage and this increases energy requirements.

Since the publication of the FAO report, new data from dietary surveys have been presented. Big people on average in fact eat no more than small people—at least in Britain (Thomson *et al.*, 1961). A possible explanation is that big people are less physically active than small people. Weight may have a sedative action. These observations may lead to a new appraisal of the relation of body weight to food requirements.

Age may affect requirements in four ways. First, there is normally a decline in physical activities with advancing age ; secondly, there is a fall in BMR ; thirdly, there may be changes in the efficiency with which muscular movements are carried out ; fourthly, changes in skill may affect the number of movements necessary to carry out a specific task. These will be discussed *seriatim.*

As people become older they tend to engage in employment which demands a smaller expenditure of energy, and also to reduce physical exercise not connected with their work. For example, miners tend to leave the heavy jobs at the coal face after the age of 45 and by 60 few remain at this type of work. When older people take lighter employment they need less food.

In the basal metabolic state and in the ' resting ' condition, the expenditure of energy per unit of body weight decreases regularly after the early twenties (Table 2, 7). This decline with age is largely due to a reduction in the proportion of metabolically active tissue in the total body mass.

In older people the efficiency and effectiveness of muscular movement may be changed, so that an older person may need more energy than a younger one for carrying out the same activity. However, this problem has not yet been widely studied.

Skill may reduce the energy requirements for a specific task. In general it may be said that an older man finds it hard to acquire new skills but maintains old skills well.

The ageing process influences caloric requirements for all three main types of activity : working, recreational and domestic, and also rest in bed. The FAO Committee recommended (with certain provisos) that, in calculating the caloric requirements of mixed populations, the general effect of ageing should be allowed for by the figures given in Table 2, 12. Again it must be emphasised that these figures apply only to large groups and not to individuals.

Climate.—Men living in a hot climate eat less food than in a cold climate. To express this relationship in quantitative terms is, however, very difficult. Quantitative studies on the influence of climate, clothing and shelter on total energy metabolism are insufficient to allow any precise conclusions to be drawn. Again, the climatic factor itself eludes exact definition, since the degree of protection from the external environment profoundly modifies the influence of climate *per se.* In a modern industrial

TABLE 2, 12. *Estimated caloric requirements of adults according to age*

(Mean annual environmental temperature, 10° C.)

Age (years)	Men weighing 65 kg.	Women weighing 55 kg.	Per cent. of requirements of Reference Man and Woman (Tables 2, 10 and 2, 11)
	Cal./day	Cal./day	
20–30 . . .	3200	2300	100
30–40 . . .	3104	2230	97
40–50 . . .	3010	2160	94
50–60 . . .	2770	1990	86
60–70 . . .	2530	1820	79
70– . . .	2210	1590	69

civilisation the tendency is to provide men and women in the factory and the home with a personal climate which is equable and comfortable and varies little throughout the year. The agricultural worker in the open, on the other hand, does not enjoy such protection. He can guard himself against cold to some extent by additional clothing, though this in itself may cause an increase in the energy cost of movement, but he has no adequate means of protection against the heat of the day. In general it may be said that an increasing number of people are being sheltered from the full impact of climate and that currently such protection is more effective against cold than heat.

The Reference Man and Woman live in the temperature zone at a mean annual temperature of 10° C. as in Great Britain. The FAO Committee recommended that the requirements assigned to the Reference Man and Woman (all other factors being the same) should be decreased by 5 per cent. for every 10° C. of mean annual external temperature above the reference temperature ; but since, as pointed out above, man is generally more able to protect himself against cold than against heat, the Committee recommended that requirements should be increased by only 3 per cent. for every 10° C. of mean annual external temperature below the reference temperature of 10° C.

CHILDREN

The caloric intake of children of different ages must obviously allow for satisfactory growth and physical development, and for the high degree of activity characteristic of healthy children. The allowances recommended overleaf take account of these facts. As need scarcely be said, it is particularly important, in the feeding of children and adolescents, to consider not only calories but their source.

Infants.—For infants of normal weight, not breast fed, from 1 month to 1 year, the U.S. Food and Nutrition Board (1953) recommended the following allowances per kilogram of body weight :

Age	Average weight	Cal./kg.
1–3 months	6 kg.	120
4–9 months	9 kg.	110
10–12 months	10 kg.	100

The allowances for breast-fed infants up to the age of 6 months are included in those of lactating mothers.

Children from 1 to 16 years.—The results of individual surveys of the food consumption of children of different ages in a number of countries support the following recommendations :

Age (in years)		Cal./day
1–3	Children :	1300
4–6	Children :	1700
7–9	Children :	2100
10–12	Children :	2500
13–15	Boys :	3100
	Girls :	2600
16–19	Males :	3600
	Females :	2400

Allowances for the ages 1 to 19 are classified into 3-year age groups in order to simplify calculations. The figures are an average for each group. If applied to a specific year of age, they should be adjusted to that age. The requirements of boys and girls have been maintained at similar levels until the age of 13. Over 13 their allowances are assessed separately. Differences in activity, size, growth rate and basal metabolic rate justify this differentiation after puberty.

Activity.—In children of all ages there are wide individual variations in activity. It must therefore be emphasised that the allowances suggested are indications for use in determining national caloric allowances and admit of considerable variation in practice with respect to small groups and individuals. Studies of the food consumption of small groups have revealed a range of intake with a coefficient of variation of ±30 per cent. of the mean, and extreme values differing from the mean to an even greater extent, particularly on the high side. The caloric expenditure of athletic children can be extremely high. At the other end of the scale, that of inactive children can be so low that they will become obese even when their caloric intake is considerably below the figures suggested above. In dealing with feeding problems involving small groups or individuals, account must be taken of activity as well as of size and age.

Two other points may be noted. The figures for girls over the age of

10 may be too high for parts of the world where social customs restrict the activities of women, since these restrictions may be imposed very early in life. In some countries children may be engaged in productive work long before growth reaches completion. Their caloric needs will be increased by such work and simultaneously they may or may not compensate for the increase by a spontaneous reduction in playtime activities.

Growth and body size.—Clearly, it is undesirable to adjust the caloric allowances of growing children to their actual weight. To attain a normal adult size, the undersized child may need more calories than the well-grown and well-developed child. For these reasons adjustments for body size should *not* be applied to the requirements of children up to the age of 16 years.

In certain parts of the world, for instance in some tropical countries, it is often difficult to regard males and females of 16 to 19 as adolescents, since at this age they may have children of their own. Caloric scales for this period of life must, however, allow for continued growth in all countries and in all social circumstances.

Climate.—Little information is available about caloric needs of children under different climatic conditions. Presumably, however, their needs will be influenced by climate in the same manner as those of adults. It is therefore recommended that the same adjustments for climate should be applied to children over 1 year of age as are applied for adults.

PREGNANCY

During pregnancy extra energy is needed for the growth of the fœtus, the placenta and associated maternal tissues, and for the increased energy expenditure involved in the movements of the heavier mother. The mother's basal metabolism also rises to reach—towards the end of pregnancy—a peak of some 20 per cent. above the usual rate for women who are not pregnant. These changes involve a total additional requirement for a pregnancy lasting 9 months of the order of 80,000 Cal., a figure based on physiological considerations applicable to all women. The extra caloric needs imposed by pregnancy can, however, be covered in two ways: either by increased food intake or by reduced physical activities. The extent to which each of these two factors contributes to ensuring energy balance during pregnancy is determined largely by social and economic factors. Thus a poor woman who already has several small children to care for, will need extra food, whereas a well-to-do primipara with few domestic responsibilities may well achieve energy balance by cutting down physical activities and so not require additional calories from food. With many women, both a reduction in activity and a modest increase in food intake are likely to take place. For calculating caloric allowances on a national scale, 40,000 extra Calories for each pregnancy is suggested.

A healthy woman of normal weight before pregnancy may be expected to gain 10±2 kg. during gestation and an increase of this order gives an indication that the caloric intake is adequate. Sudden increases in weight during pregnancy are often due to pathological causes which require medical attention. For these reasons the regular recording of weight throughout pregnancy is desirable.

LACTATION

The quantity of breast milk produced by individual women varies widely and depends on many factors, including the social environment and the physical and mental health of the mother. For the purpose of estimating requirements for lactation, the following assumptions are suggested: namely an average lactation period of 6 months and an average daily milk production of 850 ml. While satisfactory data for assessing the caloric efficiency of human milk production do not exist, it may be of the order of 60 per cent. To provide milk with a value of 600 Cal., a mother would therefore need 1000 additional Cal./day from food if her body stores are not to be depleted. This certainly applies to nursing women who have previously been undernourished or who are very active. The FAO Committee recommended an allowance of 1000 Cal./day for 6 months of lactation in estimating national average requirements.

CONCLUSION

The assessment of caloric needs and the drawing up of ration scales are practical problems. Seldom is the underlying information sufficient to allow great precision. Often other factors, economic, agricultural or social, must temper the purely physiological considerations. In all these things judgment is necessary. The account given above, as it differs only in small details from the FAO report, can be considered as orthodox. The Committee that drew up this report were unanimous in believing that the method of approach was both the most practical and at the same time the most scientific. However, there were many differences of opinion amongst members about the details. Indeed, local circumstances, changing customs and new knowledge will certainly necessitate modifications. The general principles, as laid out here, will, however, probably stand the test of time.

APPENDIX *

LETTER WRITTEN BY ANTOINE LAURENT LAVOISIER (1743–94) TO JOSEPH BLACK (1728–99), PROFESSOR OF CHEMISTRY AND MEDICINE, UNIVERSITY OF EDINBURGH.

PARIS, le 19 Novembre 1790.

M. TERRAY, Monsieur, m'a remis, en arrivant à Paris la lettre que vous m'avez fait l'honneur de m'écrire le 24 Octobre ; il ne pouvait me faire un présent qui me fût plus agréable. J'ai cru que vous ne désapprouveriez pas que je

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* *Reprinted from Brit. Ass. Adv. Sci.* (1871), p. 191 (part 1). Edinburgh.

la communiquasse à l'Academie des Sciences ; elle n'a pas moins admiré l'élegance du style que la profondeur de philosophie et la candeur qui règne dans votre lettre, et elle a même désiré qu'elle fût déposée dans ses régistres ; mais je n'y ai consenti, qu'à condition qu'il m'en serait remis une copie certifiée du secrétaire. J'ai une autre grâce à vous demander, mais sur laquelle je dois attendre votre aveu ; c'est de vouloir bein me permettre d'en publier la traduction dans les Annales de Chimie.

M. Gillan a été témoin, depuis son séjour à Paris, de quelques expériences que j'ai faites sur la respiration et il a bien voulu y concourir. Nous nous sommes assurés des faits suivans :

1° La quantité d'air vital ou gaz oxigène qu'un homme en repos et à jeun consomme, ou plutot convertit en air fixe ou acide carbonique pendant une heure est de 1200 pouces cubiques de France environ quand il est placé dans une température de 26 degrés.

2° Cette quantité s'élève à 1400 pouces, dans les mêmes circonstances, si la personne est placée dans une température de 12 degrés seulement.

3° La quantité de gaz oxigène consommée, ou convertie en acide carbonique, augmente pendant le temps de la digestion et s'élève à 1800 ou 1900 pouces.

4° Par le mouvement et l'exercise on la porte jusqu'à 4000 pouces par heure et même davantage.

5° La chaleur animale est constamment la même dans tous ces cas.

6° Les animaux peuvent vivre dans de l'air vital ou gaz oxigène, qui ne se renouvelle pas, aussi longtemps que l'on le juge à propos pourvu qu'on ait soin d'absorber, par de l'alcali caustique en liqueur, le gaz acide carbonique, à mesure qu'il se forme ; en sorte que ce gaz n'a pas besoin, comme on le croyait, pour être salubre et propre à la respiration d'être mélangé avec une certain portion de gaz azote ou Mophete.

7° Les animaux ne paroissent pas souffrir, dans un mélange de 15 parties de gaz azote et d'une partie de gaz oxigène, pourvu qu'on ait de même la precaution d'absorber le gaz acide carbonique, par le moyen de l'alcali caustique, à mesure qu'il est formé.

8° La consommation du gaz oxigène et sa conversion en acide carbonique est la même dans le gaz oxigène pur et dans le gaz oxigène mêlé de gaz azote, en sorte que la respiration n'est nullement accélérée en raison de la pureté de l'air.

9° Les animaux vivent assez longtemps dans un mélange de deux parties de gaz inflammable et d'une de gaz oxigène.

10° Le gaz azote ne sert absolument à rien dans l'acte de la respiration et il ressort du poumon en même quantité et qualité qu'il y est entré.

11° Lorsque par l'exercise et le mouvement on augmente la consummation de gaz oxigène dans le poumon, la circulation s'accélère ; ce dont il est facile de s'assurer par le battement du poulx ; et en général lorsque la personne respire sans se gêner, la quantité de gaz oxigène consommée est proportionnelle a l'augmentation du nombre des pulsations multiplié par le nombre des inspirations.

Il est bien juste, Monsieur, que vous soyez un des premiers informés des progrès qui se font dans une carrière que vous avez ouverte, et dans laquelle nous nous regardons tous comme vos disciples. Nous suivons les mêmes expériences, et j'aurai l'honneur de vous fair part de mes découvertes ultérieures.

J'ai l'honneur d'être avec un respectueux attachement, Monsieur,
Votre très-humble et très obéissant Serviteur,

(Signed) Lavoisier.

CHAPTER 3

APPETITE AND SATIETY

THE physiological mechanisms by which a man's food intake is regulated to his energy expenditure, and his weight maintained constant, have been strangely neglected by physiologists until recently. It is now known that food intake is determined by regulatory centres in the brain, which co-ordinate a variety of sensory stimuli arising from other parts of the body.

The precision with which food intake is regulated will be realised when it is remembered that in the course of 25 years of varied activity a man can eat 12 tons of food and yet his weight throughout the whole of this time may never vary by more than 2 or 3 lb. This represents an overall accuracy of adjustment of about 0·05 per cent. A very slight maladjustment of the regulatory mechanism over the years can lead to a considerable degree of obesity.

Although food intake over long periods is very precisely adjusted to caloric needs, the adjustment is not so accurate from day to day. It is a common experience that a sudden change of habit from a sedentary to an active life or *vice versa* is not immediately followed by the necessary change in food intake. Measurements of the food intake of a group of students, who undertook a period of 5 days of hard exercise between two periods of artificially restricted sedentary life, showed that in none of the students did the food intake change abruptly with the changes in energy expenditure (Passmore *et al.*, 1952). During this experiment one of the subjects developed mumps, which restricted his food intake for four days. Fig. 3, 1 shows that for this subject, over a period of 13 days, energy intake equalled energy expenditure despite large daily fluctuations in the caloric balance. In the previous chapter reference was made to surveys in which the caloric values of the food intake and of the daily energy expenditure were measured simultaneously. Durnin (1961*a*) has analysed the results in six different groups of subjects. There was usually good agreement between the average daily energy intake and output over the whole week in each subject, although there was little or no correspondence between intake and expenditure on any one day. It appears that some people can incur a debt or surplus of up to 2000 Cal. or even more before the necessary dietary adjustment is made. There would appear to be some long-term mechanism controlling body weight, in addition to daily changes in appetite.

PSYCHOLOGICAL FACTORS

It has been fashionable to ascribe all disturbances of appetite to psychological causes. This in fact equates obesity with the sin of gluttony, as indeed is sometimes the case. It is, of course, well known that psychological diseases can profoundly affect appetite. Anorexia nervosa, which is a rare disorder, can lead to subnutrition and even death from starvation. It is almost always due to a severe psychological upset. While some obese people may become fat as a result of a neurotic disorder, in the majority there is no evidence of such a disturbance. It is our experience that obese people belong to a variety of psychological types and many of our obese friends appear to have very well-balanced personalities. A disturbance of physiological rather than psychological mechanisms regulating food intake must be postulated. These mechanisms will now be considered.

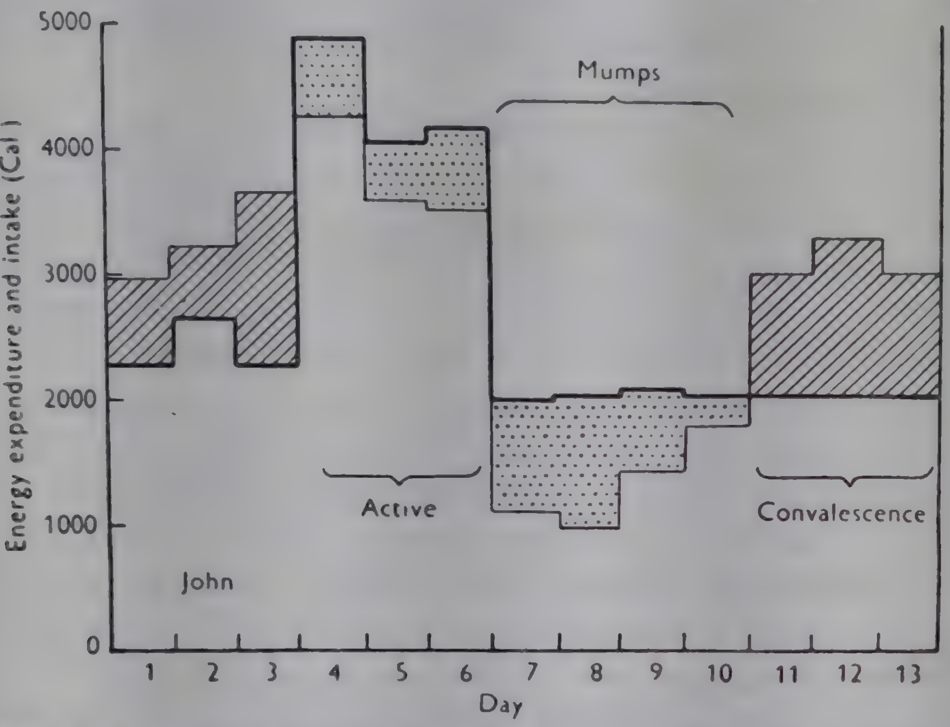


FIG. 3, 1. Energy balance in a young man during four periods: (*a*) 3 days—sedentary life; (*b*) 3 days—activity; (*c*) 4 days—mumps; (*d*) 3 days—convalescence. Thin line=daily energy intake; thick line=daily energy expenditure. Cross-hatched areas show excess intake over expenditure; stippled areas show excess expenditure over intake.

THE FEEDING REFLEXES

Feeding is a reflex activity co-ordinated by centres in the brain. A variety of sensory stimuli, some nervous and some chemical and perhaps even thermal, impinge on these centres and so determine subsequent behaviour.

The feeding centres in the hypothalamus

It has long been known that obesity can arise from the effects of tumours at the base of the brain in the region of the pituitary gland and hypothalamus. Over 50 years ago this condition was described by Fröhlich, an Austrian physician. At one time it was thought that Fröhlich's syndrome was attributable to a failure of secretion of the anterior pituitary gland.

However, it is now recognised that the essential cause of this type of obesity is a disturbance of the hypothalamic region in the base of the brain adjacent to the pituitary gland. This indeed was a possibility that Fröhlich himself discussed. Work on animals has amply confirmed this view. Brobeck *et al.* (1943) at Yale, and Kennedy (1950) in London, showed that it was possible to disturb profoundly the feeding behaviour of rats by injuring the brain in this region. Using stereotaxic instruments, it is now possible to produce microscopic lesions in the brain, which can be accurately located. Anand *et al.* (1955) in Delhi extended this work to cats and monkeys. They found that if the lateral nuclei of the hypothalamus were destroyed in these animals, feeding ceased. This they attributed to destruction of a feeding centre. If the medial nuclei of the hypothalamus were destroyed, overfeeding followed, attributable to destruction of a satiety centre.

This evidence from experimental animals, with some confirmation from human pathology, leaves no room to doubt that feeding behaviour is co-ordinated by nerve centres at the base of the brain, which can be accurately located and the dimensions of which are measured in millimetres. Anand (1961) has reviewed the nervous regulation of food intake. What are the stimuli that impinge on these controlling centres ?

1. **Nervous stimuli.**—The hungry man can sometimes feel his stomach contracting. By swallowing a small balloon and inflating it in the stomach it is possible to record these hunger contractions. They are found only in association with hunger, but do not appear consistently in all subjects. They cease after the intake of food. It is possible to denervate the stomach completely in experimental animals without disturbing their feeding habits. Surgeons have carried out a great variety of operations on the human stomach, in many of which scant respect has been given to the nerve supply of the organ ; yet disturbances of appetite seldom follow gastric operations. The conclusion is that nervous stimuli from the stomach play only a subsidiary role in stimulating feeding centres.

2. **Chemical stimuli.**—There are at least two chemical substances whose level in the blood is closely associated with appetite—glucose and nonesterified fatty acids (Chapter 6).

GLUCOSE.—In many hungry people the blood glucose level is low. Absolute levels of blood glucose, however, cannot explain appetite : otherwise the diabetic patient with his high blood glucose would never be hungry. In fact, he may be ravenous when his blood glucose is very high indeed. To overcome this difficulty Mayer (1953 *a*) has devised an ingenious hypothesis, based on observations summarised in Fig. 3, 2 (Mayer, 1953 *b*). He has taken the difference between glucose levels in arterial (A) and venous (V) blood as a measure of the ' effective ' blood glucose, *i.e.* the amount of glucose in the blood that is in a condition to enter the cells. When this A-V difference is high, as after a meal, presumably glucose is being rapidly metabolised by peripheral tissues. There must be a high level of ' effective ' glucose in the arterial blood ;

this acts on the cells in the feeding centre and suppresses hunger. Four hours after a meal the A-V difference becomes very small and hunger develops. In diabetic patients A-V differences are usually small, despite high total blood glucose levels, and these small differences may determine hunger. In healthy and sick people under a variety of conditions, and in experimental animals, Mayer found that an A-V difference greater than 10 mg. of glucose/100 ml. of blood was never associated with hunger. Levels tending towards zero for a sufficient time were associated with the sensation of hunger. There is little doubt that Mayer's conception of a low level of ' effective ' blood sugar as a stimulus to feeding is correct and it is an important contribution to the theory of the chemical control of appetite.

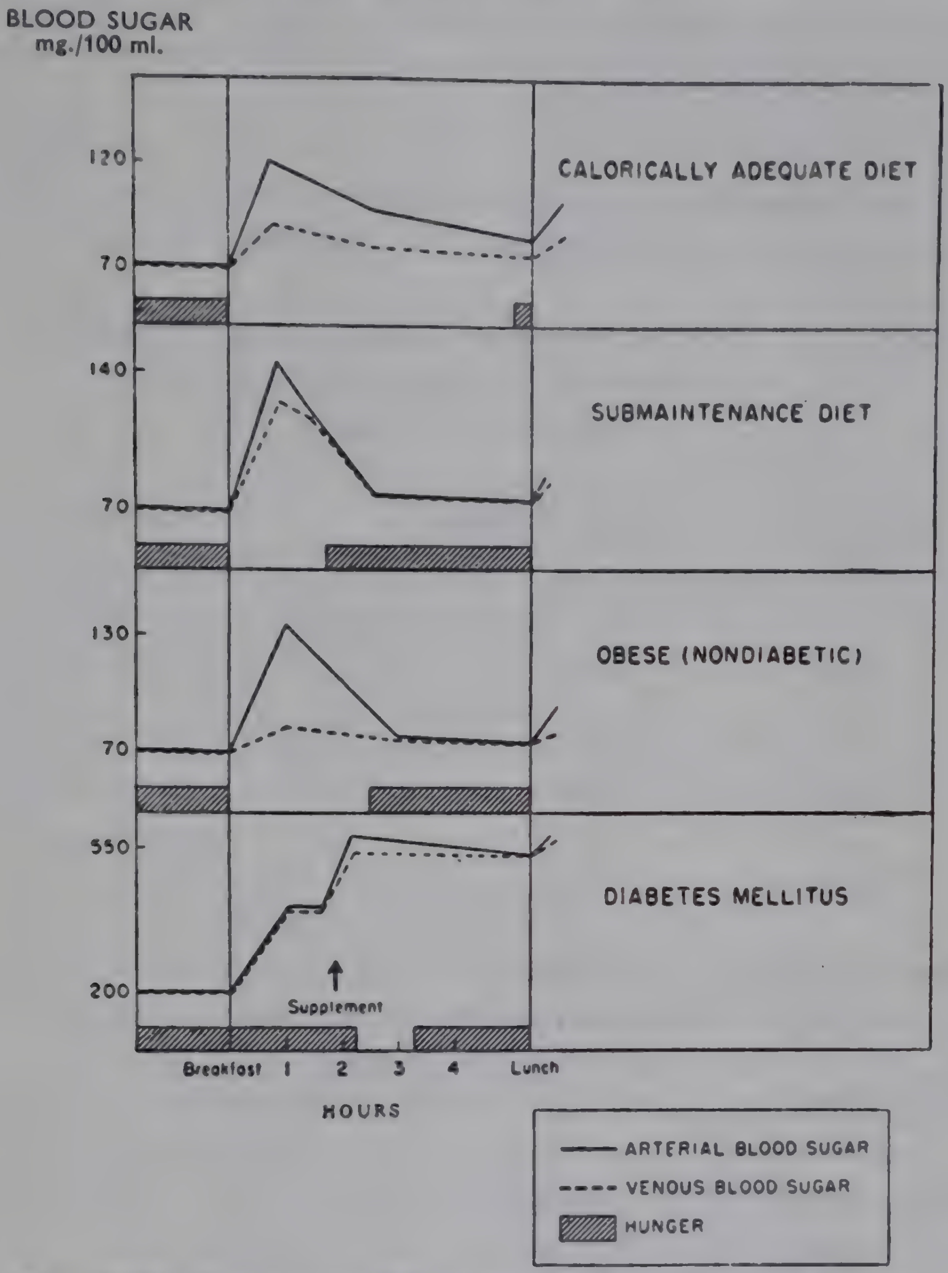


FIG. 3, 2. Correlation of hunger with the differences between glucose in arterial and venous blood. No hunger feeling appears if the difference is greater than 10 mg./100 ml. (From MAYER, 1953 *b*).

NONESTERIFIED FATTY ACIDS (NEFA).—The level of NEFA in the blood is closely related to the immediate nutritional state (Gordon &

Cherkes, 1956). Before a meal, when a person is hungry, the level is high. This is presumably due to increased mobilisation of depot fat, consequent upon the utilisation of all the carbohydrate in the previous meal. This high level might well be a signal to the feeding centre. After a meal or after ingestion of glucose, the level falls rapidly. This low level might be a signal to the satiety centre. Certainly the association between hunger and appetite and plasma NEFA level is close, but whether it is part of a regulatory mechanism is uncertain.

3. **Thermal stimuli.**—Brobeck (1948 and 1957) has developed the hypothesis that increased heat production is an important signal to the satiety centre. In brief, he postulates that " animals eat to keep warm and stop eating to prevent hyperthermia." He showed that rats kept at a temperature of 94° F. eat a diet containing only 12 Cal./day, whereas rats kept at 72° F. eat a diet containing 48 Cal./day.

TABLE 3, 1. *Specific dynamic action (SDA) of food eaten in 18 hours when lard was added to diet*

Male rats (300–325 g.)

Lard added to diet	Total caloric intake	Partition of caloric intake			Calculated SDA			
		Protein	CHO	Fat	Protein	CHO	Fat	Total
Per cent.	Cal.	Cal.	Cal.	Cal.	Cal.	Cal.	Cal.	Cal.
0	54·8	13·2	36·7	4·9	4·0	1·8	0·2	6·0
14	66·4	11·0	30·9	24·5	3·3	1·5	1·0	5·8
43	90·0	7·2	19·8	63·0	2·2	1·0	2·6	5·8
57	116·3	5·8	17·5	93·0	1·7	0·9	3·8	6·4

Strominger and Brobeck (1953) found that rats fed *ad lib.* ate more food when the proportion of fat to protein in the diet was steadily increased ; so that their caloric intake could be doubled in this way (Table 3, 1). Fat has a very small specific dynamic action as compared with protein. The rats chose diets which had a constant SDA independent of their caloric value. This is explicable on the hypothesis that the feeding centres in the hypothalmus were sensitive to very small changes in heat production. Passmore and Ritchie (1957) showed that in man the SDA of a meal could be demonstrated immediately after the cessation of feeding and that no latent period for its effect was observable. Clearly in man the extra heat production from the SDA of a meal could be the cause of the satiety associated with the end of eating.

DISCUSSION

As Brobeck has pointed out, there is a useful analogy between the control of respiratory movements and the control of feeding. Respiratory movements are regulated by centres in the brain-stem responding to a variety of stimuli : some nervous and some chemical. The sensitivity of the centres is known to be affected by changes in temperature. The centres in the hypothalamus may well regulate feeding behaviour in response to a similar variety of stimuli. Gastric motility, arteriovenous glucose difference and heat production are three factors that can be measured, and changes in each have been associated with changes in feeding behaviour. But these three by no means exhaust the list of possible regulating factors.

For instance, could there not be receptors in the body sensitive to the total body mass ? Dodds (1950) has suggested that gravity may be a controlling factor. He has attempted to buoy up thin people with balloons in the hope that the consequent reduction in their gravitational pull would increase their food intake. He also hoped that he might be able to reduce the food intake of fat people by weighting them with sandbags. As he says, these experiments caused his colleagues to doubt his sanity. But the idea of a physical control of body mass is not intrinsically absurd, although we know of no evidence to support it. Control there must be, but it seems more plausible to postulate a chemical mechanism and that the total body content of fat, of protein and perhaps of other substances may be regulated by some chemical feed-back mechanism, of which the appetite is an integral part. How the total mass of fat or other substances in the body normally regulates feeding behaviour it is impossible to state.

Factors that determine chemical pathways might also determine appetite, and differences in chemical behaviour of animals may provide clues to the central problem. In a precise experiment illustrated in Fig. 3, 3, Greenbaum (1953) has shown that under the influence of pituitary growth hormone rats make different *use* of the *same* food. Probably the hormone stimulates the catabolism of fat and so spares protein, which is then available for growth.

The liver undoubtedly has an important role in determining appetite. When the liver is damaged—as occurs in infectious hepatitis—there is usually an immediate loss of appetite. This is often the predominant symptom, which may also be present in other infections associated with some degree of liver damage. After a meal the flow of blood in the portal circulation is increased and it carries a large load of absorbed nutrients to the liver. The liver quickly produces metabolites from these, which are passed on to the general circulation and so to the feeding and satiety centres in the brain.

Mayer has made an extensive study of obesity in mice. He has shown that there are important chemical differences between different types of obesity. Mice can be made obese by hypothalamic injury : it is also possible to study obese mice, whose obesity is determined genetically by a recessive gene. Whereas the normal weight for an adult mouse is about 30 g., both of these types of mice may weigh up to 100 g. and the excess is due almost entirely to fat. After hypothalamic injury the mouse develops a voracious appetite, and lays down the excess food as fat. The genetically obese mouse may eat little more than the normal mouse. He gets fat by reducing all spontaneous movement by just sitting quietly in his cage. He has a marked disturbance in his carbohydrate utilisation with a raised blood sugar, giving rise to diabetes which is resistant to insulin. The carbohydrate metabolism in the mouse made fat by hypothalamic injury is normal. The genetically obese mouse has marked differences in the utilisation of metabolites. If radioactive acetate is injected into these animals, the fate of the ^{14}C carbon atoms can be followed. Mayer has shown that these animals excrete significantly less carbon dioxide than normal controls and that a higher proportion is incorporated into fat, both in the liver and adipose tissue. Even if food intake is drastically reduced, ‘ lipogenesis ’ is observed and under all circumstances these animals seem to build up fat rather than catabolise it. Hypothalamic obese rats do not show this abnormality or do so in a very small degree. It seems clear that in one type of obesity in the mouse there is a very marked abnormality in fat metabolism.

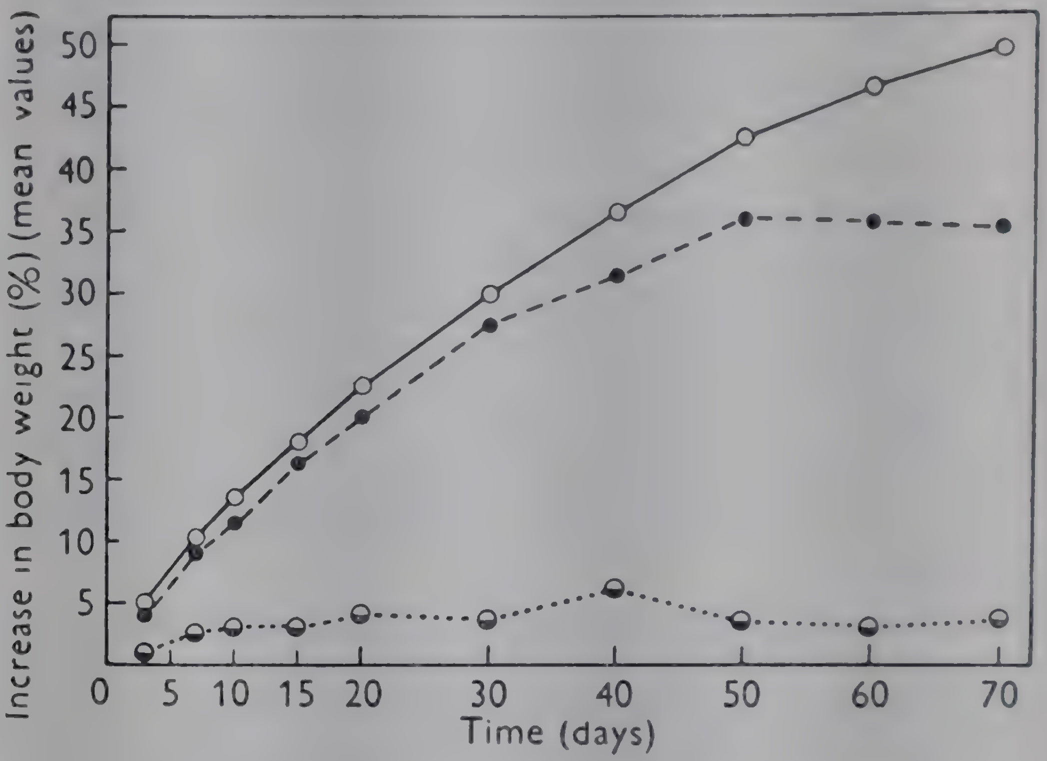


Fig. 3, 3. Growth curves of normal rats (◒) and rats treated with growth hormone (*a*) on unlimited food intake (○), and (*b*) on same intake as the control rats (●).

Many people in middle life increase their stores of body fat, and the consequent gain in weight results in an increased liability to a variety of diseases. The setting of the mechanism controlling appetite has been altered and the new adjustment is not for the better. Mayer (1955) has suggested that for the accurate regulation of the appetite a certain minimum amount of physical exercise is necessary. As a result of the changes in the way of life discussed in Chapter 2 more and more people are becoming so sedentary that their physical activities fall below this minimum. He writes: " Inactivity may be the most important fact explaining the frequency of ' creeping ' overweight in modern Western societies. Natural selection, operating for hundreds of thousands of years, made men physically active, resourceful creatures, well prepared to be hunters, fishermen or agriculturalists. The regulation of food intake was never designed to adapt to the highly mechanised sedentary conditions of modern life, any more than animals were made to be caged." Fig. 3, 4

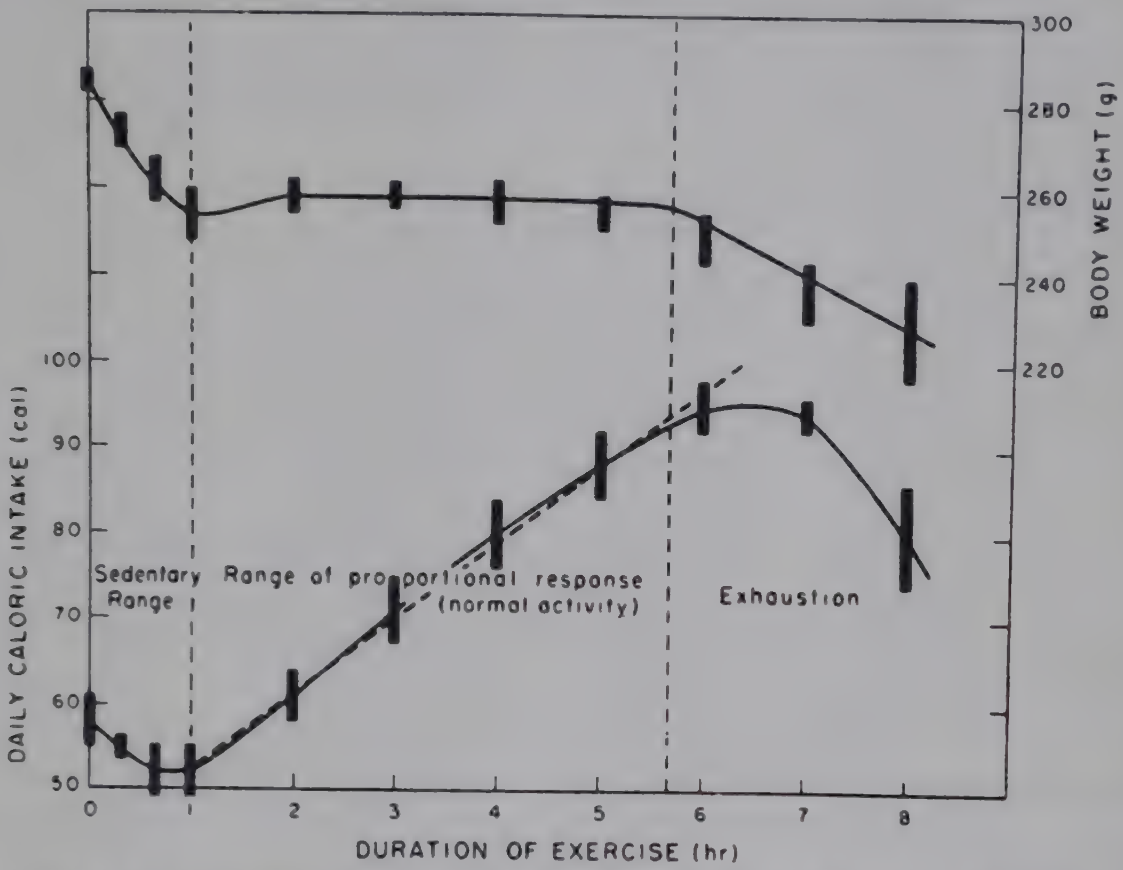


FIG. 3, 4. Voluntary caloric intake and body weight as a function of exercise in normal rats. The exercise was carried out on a treadmill.

(Mayer *et al.*, 1954) gives the results of an experiment on rats that supports this contention. Groups of rats were exercised on a treadmill for periods of up to 8 hours daily. If exercise lasted between 1 and 6 hours, food intake was regulated in direct proportion to the length of the period of exercise and the animals' weights remained steady. If the exercise lasted more than 6 hours they were too tired to eat and their weights fell. But if the period of exercise was less than 1 hour the animals ate more food than was necessary and so became obese. It is postulated that for these rats 1 hour of exercise each day was needed to set the appetite-regulating mechanisms. If this concept is applicable to man, then the prescribing of exercise may be as important in a reducing regime as the prescribing of diets. This is discussed further in Chapter 27.

In conclusion an apology is perhaps needed for the discursiveness of this chapter. That the regulation of food intake is an important and complicated physiological mechanism has only recently been generally appreciated. The awakening of interest has led to much ingenious speculation and the carrying out of a few well-planned experiments. These have for the most part brought to light not a clear solution of the problem but further difficulties. No straightforward or simple account of appetite and satiety mechanisms is possible at the present time.

CHAPTER 4

CARBOHYDRATES

CARBOHYDRATES provide most of the energy in almost all human diets. In the diets of poor people, especially in the tropics, up to 90 per cent. of the energy may come from this source. On the other hand, in the diets of the rich, especially in the U.S.A., the figure may be less than 50 per cent. Neither of these extremes is generally desirable. Probably 55 to 65 per cent. is a suitable figure for most good normal diets.

It has been said in Chapter 2 that green plants can synthesise carbohydrate from water and carbon dioxide under the influence of visible light. Part of this carbohydrate goes to make the supporting structures of the plant—the fibre or wood which are largely composed of cellulose ; a part provides energy for growth, and a further part may be stored as sugars or starch. These stores provide for the caloric needs of the plant during times when photosynthesis is dormant, and for its seeds, which contain a store of carbohydrate for the nutrition of the embryo until energy is again available from photosynthesis. Man and his ancestors have been remarkably successful in seeking out and latterly cultivating various seeds, fruits and roots which contain concentrated supplies of carbohydrate. Undoubtedly this has been a cardinal factor in his evolutionary development. Ruminants such as sheep have no particular powers of selecting or conserving vegetable foods rich in carbohydrates and so, to satisfy their caloric needs, must spend the greater part of their life chewing grass—a food that is 80 per cent. water. Man, on the other hand, by his successful cultivation, particularly of cereal grains, can lay up a store of food from which he can quickly obtain sufficient energy and have time left for other things.

CHEMISTRY

The carbohydrates are a class of chemical compounds composed of carbon, hydrogen and oxygen. In general they contain 2 atoms of hydrogen for each atom of oxygen ; the same ratio as in water. Sugars and starch are carbohydrates, as also is cellulose which forms the bulk of the undigested roughage in human food. Pigman (1957) has written an excellent monograph on the chemistry of carbohydrates.

The following carbohydrates are known to be concerned in human nutrition and metabolism.

MONOSACCHARIDES

These are the simplest sugars containing from 3 to 6 atoms of carbon in each molecule. They are called trioses, tetroses, pentoses, hexoses, according to whether they contain 3, 4, 5 or 6 carbon atoms. Only the hexoses occur in appreciable amounts in human foods.

Hexoses

Glucose (dextrose, grape sugar).—This is the only hexose sugar known to exist in the free state in the fasting human body ; it is present in the blood in a concentration of about 0·1 g./100 ml. Glucose is a white crystalline solid, freely soluble in water with a mildly sweet taste. Its chemical structure is shown in Fig. 4, 1.

Because of the asymmetrical carbon atoms in the molecule, solutions of glucose rotate polarised light. The rotation is to the right, hence the alternative name—dextrose—which is often used in industry. This property can be used to distinguish glucose from fructose (see below). Glucose is a reducing agent ; its power of reducing copper compounds from the cupric to the cuprous state is the basis of Benedict's and Fehling's tests for detecting glucose in the urine. The reductions of potassium ferricyanide to ferrocyanide and of Cu^{++} to Cu^{+} are the basis of reliable methods for estimating glucose in the blood.

Few natural foods, except some fruits such as grapes, contain more than traces of free glucose. However, starch consists of glucose in combined form and glucose is also a principal constituent of sucrose and some other sugars (see below).

Glucose manufactured from starch is sold commercially in a variety of relatively expensive proprietary preparations as a dietary adjunct ; there is no evidence, however, that it possesses any important therapeutic advantage over sucrose when fed by mouth.

Fructose (lævulose, fruit sugar) has the same empirical formula —$C_6H_{12}O_6$—as glucose, but its structure is different, as shown in Fig. 4, 1. Fructose is found in free form in some fruits and also in honey ; it is a constituent of many more complex carbohydrates. It rotates polarised light to the left ; hence its alternative name—lævulose.

Galactose is a hexose that is present in bound form in lactose (milk sugar) and in many plant polysaccharides.

Mannose is a hexose of more interest to sugar chemists than nutritionists ; small amounts are found in certain foods such as manna, from which it takes its name. Manna is the dried sap of certain species of ash and other trees, including the tamarisk which grows in the Sinai Desert.

Hexose derivatives

Sorbitol (D-glucitol) is an alcohol which is made commercially from glucose by hydrogenation. By this means the aldehyde (CHO) group in the glucose molecule is changed to an alcohol (CH_2OH) group (Fig. 4, 1). Though sorbitol is found in some fruits (such as rowan berries), it is chiefly the factory product that finds a use in dietetics. At least 90 per cent. of ingested sorbitol is absorbed and metabolised, probably after conversion to glucose, as experiments with tracers have shown (Adcock &

HEXOSE SUGARS AND SOME DERIVATIVES

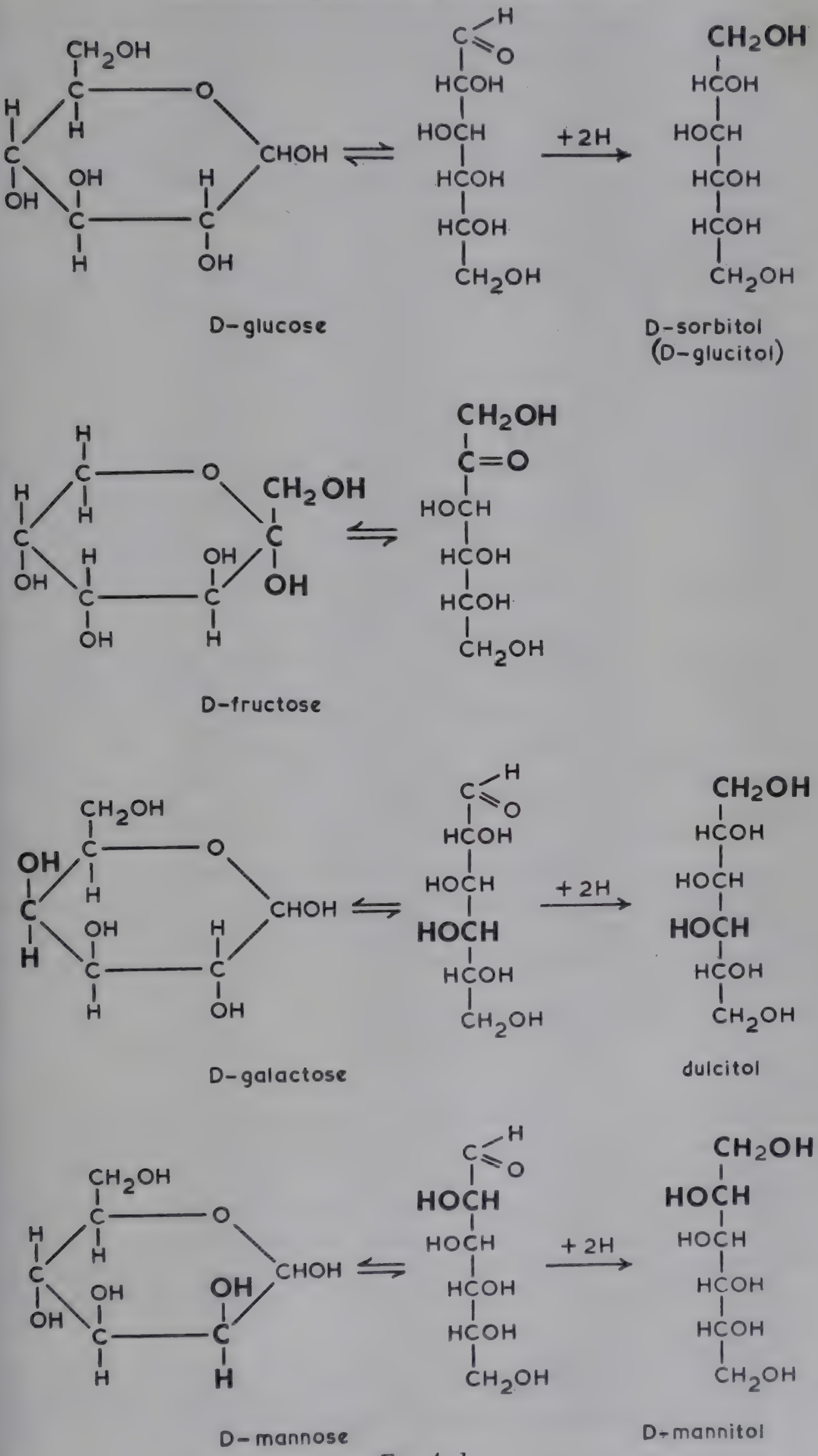
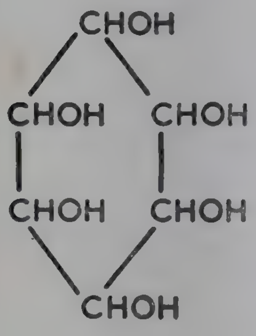


FIG. 4, 1

Gray, 1957). However, its rate of absorption from the gut is so much slower than that of glucose that it has little effect on the blood sugar level. The slow intestinal absorption of sorbitol, combined with its mildly sweet flavour (said to be 60 per cent. of the sweetness of sucrose), has given it a wide use in the manufacture of ‘ diabetic ’ jams, marmalade, tinned fruits, fruit drinks and chocolate. Such foods may be helpful to a diabetic. However, as sorbitol is both expensive and calorigenic, its use in practice is limited.

Mannitol and **Dulcitol** are also obtained by hydrogenation of mannose and galactose respectively, in the same manner as sorbitol from glucose. Mannitol is also extracted commercially from sea-tangle (*Laminaria*), the long, ribbon-like seaweed that grows just below the low-tide line round the coasts of Great Britain. These sugars have a variety of industrial uses and are sometimes employed in the manufacture of foods as improvers. It should be mentioned, however, that mannitol, dulcitol and to a lesser extent sorbitol cause diarrhœa if taken in excess, presumably because they may pass undigested into the large intestine and there undergo bacterial fermentation. Moreover, they help to keep the bowel contents fluid by their osmotic effect.



inositol

FIG. 4, 2

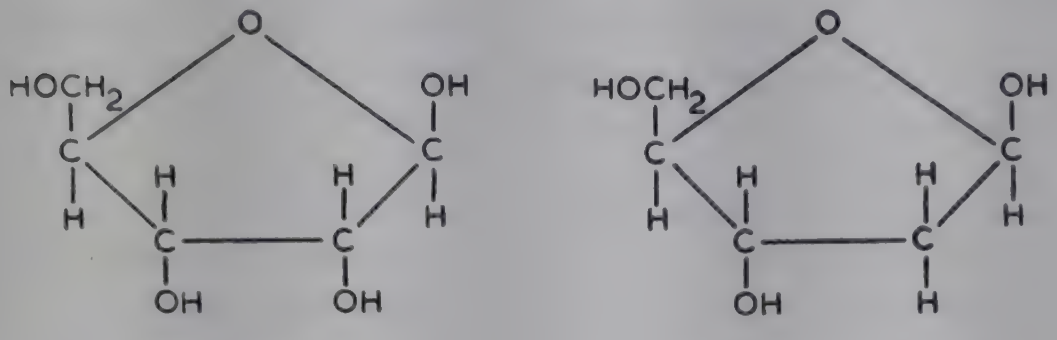
Inositol is an alcohol in some ways allied to the hexoses and therefore deserves mention here. Its structural formula is shown in Fig. 4, 2. It occurs in many foods and especially in the bran of cereal grains. Inositol in combination with 6 phosphate molecules forms the compound *phytic acid* which hinders intestinal absorption of calcium and iron (Chapter 11). Inositol has sometimes been classified as a vitamin because mice require traces of it in their diet ; but there is no evidence that it is an essential nutrient for man ; moreover its wide distribution in foodstuffs of all kinds makes it most unlikely that deficiency of inositol could ever occur, even supposing that it is necessary.

Ascorbic acid (Vitamin C) is structurally related to the hexose sugars.

Pentoses

Dietetically, the 5-carbon sugars are of little or no importance as a source of energy for the body ; yet their derivatives are present in small amounts in all cells, whether animal, plant or bacterial. The pentoses concerned are **D-ribose** and **D-2-deoxyribose** whose structural formulæ are shown in Fig. 4, 3. These sugars are essential components of the nucleoproteins and of high-energy compounds such as ATP (Chapter 9). They are synthesised by all types of animals as well as man and are not essential in the diet.

The pentose sugars most commonly present in human foods are **L-arabinose** and **D-xylose** which are widely distributed in fruits and root vegetables. So far as is known, however, neither of these sugars occur in animals and it is not known whether they are digestible. Pentose sugars fed by mouth to human subjects have been recovered almost quantitatively from the urine and fæces. Furthermore, there is experimental evidence to show that ribose and deoxyribose can be synthesised within the human body from any other of the sugars in the tissues, all of which are interconvertible.



D-ribose D-2-deoxyribose

FIG. 4, 3

DISACCHARIDES AND TRISACCHARIDES

Sucrose (cane sugar, beet sugar) is the familiar sugar in common domestic use. It is derived from one molecule of glucose combined with one molecule of fructose with loss of one molecule of water. The two moieties are split apart by hydrolysis in the process of digestion and also by the action of acids in the laboratory or factory. Sucrose itself rotates polarised light to the right, but since fructose is more lævo-rotatory than glucose is dextro-rotatory, hydrolysis of a sucrose solution changes the rotation to the left. Hence the hydrolysis of sucrose (which takes place very readily) has been described in the past as ‘ inversion.’ ‘ Invert sugar ’ is the commercial name for the product, which is a mixture of glucose and fructose.

Sucrose is widely manufactured by extracting it from two easily cultivated natural sources ; sugar cane and sugar beet.

Lactose is the principal sugar present in milk and is unique to mammals. Like sucrose it is derived from two monosaccharides linked together, one of which is glucose and the other galactose.

Maltose.—This too is a disaccharide, in this case derived from two linked molecules of glucose. As its name suggests, it is formed from the breakdown of starch in the process of malting barley.

Raffinose is a trisaccharide of glucose, fructose and galactose ; it is found in molasses.

POLYSACCHARIDES

The three polysaccharides most important to man—starch, glycogen and cellulose—are all polymers of glucose ; *i.e.* they are made up of many molecules of glucose, linked together. In contrast to the sugars already mentioned, they are tasteless.

Starch is the form in which utilisable carbohydrate is stored in granules within the seeds and roots of many varieties of plants. The starch grain usually contains two polysaccharides derived from glucose. The first, comprising about 15 to 20 per cent. of the total starch, is a long unbranched chain of several hundred glucose units and is known as amylose. Amylose is responsible for the intense blue colour resulting on the addition of a trace of iodine to suspensions or solutions of starch. The major component of starch is known as amylopectin ; it is a highly branched glucose polymer and, if free from amylose, gives a brownish violet colour on the addition of iodine. Some varieties of grains such as the ‘ waxy ’ variants of maize and rice, contain virtually no amylose. Starch grains, as obtained freshly from plants, are completely insoluble in water. Heat, however, promotes a solution which remains fairly stable, although it may form a jelly on cooling.

As has been said, plants store their starch in the form of microscopic granules, each composed of many millions of individual starch molecules. When a section of raw potato or other starchy vegetable is viewed under the microscope, the starch granules are seen to be lying in groups, within the thin-walled cells of the plant. Moist heat causes the starch granules to swell and rupture the cells. Thus cooking renders the starches in vegetable foods more available for digestion.

The starch molecule is broken down in the human digestive tract to form maltose and ultimately glucose. The molecule is also slowly broken down in the process of cooking, if temperatures considerably above the boiling point of water (100° C.) are used. Thus when starchy foods are grilled or fried, or when barley is malted, some maltose and even glucose may be split off from the starch molecule. In addition, a large number of intermediate degradation products of starch may be formed ; these are commonly called *dextrins* ; but they have no precise chemical formula and are simply portions of the original starch molecule, of varying sizes. **Caramel** is another carbohydrate product of indefinite composition ; it is formed when sugars of any kind are partially broken down by high temperatures. Its brown colour, slightly burnt flavour and sticky consistency make it a valuable adjunct to the art of the good cook.

Cellulose.—The fibre on which green plants depend for support is mainly composed of cellulose. Wood contains cellulose, hemicelluloses and lignin—a high-molecular polyphenol. Hemicelluloses are formed from glucose, galactose, xylose and uronic acid. Cellulose, like starch, is made entirely of glucose ; the molecule consists of 3000 or more glucose units held together in long chains. In contrast to starch, cellulose does not disperse in water and is extremely resistant to hydrolysis by acids and enzymes.

Herbivorous mammals are able to obtain energy from cellulose and hemicelluloses by virtue of the activity of cellulose-splitting bacteria and protozoa in their rumen or cæcum. Man has no such powers, consequently the fibres of vegetable foods form the bulk of the roughage that passes undigested through the human intestinal tract.

A chemical product of cellulose—*methyl cellulose*—is in current use as an inert, bulky material that will fill the stomach and thus may help to allay the pangs of hunger of patients on a reducing diet.

Glycogen.—This is the animal equivalent of starch and is found in human tissues. The glycogen molecule is composed of 3000 to 60,000 glucose units built up in branching chains, each branch consisting of 12 to 18 glucose units. Unlike starch grains, glycogen dissolves in water ; it is readily broken down by the appropriate enzymes to yield glucose. Animal livers and shellfish are the richest natural sources. An oyster (removed from its shell) usually contains about 6 per cent. (wet weight) of glycogen.

Other polysaccharides in human food

Inulin takes the place of starch in some plants ; it is composed of about 40 fructose units terminated by one of glucose. It is found in the leaves and tubers of *Compositæ* such as artichokes and dahlias. It has no nutritional importance but is familiar to physicians since it is used in one of the established tests of renal function.

Pectin (or more properly pectic acid) is a polysaccharide found in small quantities in many fruits, young green plants and root vegetables (*e.g.* turnips). Under appropriate conditions—in the presence of sugars and a warm, slightly acid dilute solution—it turns into a jelly. This useful property is responsible for the setting of properly made jams and fruit preserves.

Seaweed polysaccharides.—These include *agar* (a polymer of galactose) used by bacteriologists, and as a food by the Japanese, and *alginic acid* composed of polymerised mannuronic acid (see below). Because of their property of forming jellies, they are sometimes used by manufacturers as food additives to alter the texture or consistency of artificial foods such as ice-cream. Alginic acid has the useful property of forming jellies without the need for heat and is the essential ingredient in several modern quick-mix jelly preparations. Carrageen ' moss ' is a seaweed used as a food on the coasts of Scotland and Ireland. It contains polysaccharides which set to a firm jelly on cooking. Carrageen incidentally is rich in sulphate and other minerals. Nothing is known of the digestibility of these polysaccharides.

Chitin is the material that forms the organic base for the hard parts of insects and crustacea and is also present in mushrooms and other fungi. The shards of crabs and lobsters are impregnated with calcium carbonate, which can be dissolved away by acids, leaving the rubbery chitin. This is a cellulose-like compound, but built out of units of glucosamine (see over) instead of glucose. Like cellulose, chitin is insoluble and indigestible.

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CARBOHYDRATE COMPOUNDS OCCURRING IN THE HUMAN BODY

Many complex compounds containing carbohydrates are found in the human body. So far as is known they are entirely endogenous in origin, *i.e.* synthesised within the body, and so have little immediate interest for the nutritionist. Nevertheless, they deserve brief mention here since they have many important medical implications.

The nucleic acids, which contain ribose and deoxyribose, are discussed in Chapter 8. Glycogen has already been mentioned on the previous page.

Uronic acids.—Hexose sugars can undergo oxidation at one of their carbon atoms with the introduction of a carboxyl (COOH) group. *Glucuronic acid* derived in this way from glucose has considerable biological importance since it is present in mucoproteins and the polysaccharides made by bacteria (see below). Moreover, numerous toxic substances are eliminated from the human body in combination with glucuronic acid and so excreted in the urine.

Hexosamines.—The amino group (NH_2) can replace a hydroxyl (OH) group in the hexose molecule. Glucosamine is widely distributed in nature, in many polysaccharides including those of bacteria and the specific substances in human blood that determine the blood groups. Consequently the chemical behaviour of hexosamines is of considerable interest. They are present in human milk.

Mucopolysaccharides.—These are complex polysaccharides composed of hexoses, uronic acids and hexosamines. Examples are :

HYALURONIC ACID is a polysaccharide containing equimolecular amounts of glucuronic acid and glucosamine. It forms a highly viscous solution in water and acts in the human body as a protective and lubricating factor. It is found in the synovial fluid of joints and in the vitreous humor of the eyes, to the extent of about 0·03 per cent. It also forms a protective coating round the unfertilised ovum. Its sulphuric acid ester, known as *mucoitin sulphate*, is found in mucus (see below). Certain bacteria, notably the streptococci, apparently protect themselves with hyaluronic acid. The acid is broken down by an enzyme, *hyaluronidase*, which thereby reduces surface tension and hence is a spreading factor. Hyaluronidase occurs naturally in semen, in the venom of some snakes and insects and in some bacteria, notably the pneumococcus and the gas-gangrene organisms (*Clostridia*).

CHONDROITIN SULPHATE is the sulphuric acid ester of a polysaccharide containing galactosamine and glucuronic acid. It is found in cartilage, the organic matrix of bone and in the umbilical cord.

HEPARIN is a polysaccharide resembling hyaluronic acid with a large number of sulphate groups ; it is an anticoagulant present in the liver, lungs and other tissues. It also influences the fat content of the blood (Chapter 6).

The **Cerebrosides** are a group of complex fatty substances, mentioned again in Chapter 6. They are found in the brain, the myelin sheath of nerves and in other tissues; they include *phrenosin*, *cerebrin* and *kerasin*. Their interest here is that their chemical structure includes a hexose sugar, sometimes glucose but usually galactose.

Mucoproteins.—These are proteins that have small but important amounts of polysaccharides attached to them. A good example is the mucus that is secreted by the gastric mucosa and protects it from digestion by its own proteolytic enzymes. Gastric mucus also contains mucoitin sulphate.

Comment

Many of these complex carbohydrate-containing compounds have obvious importance in the human body: yet the amounts present both in human tissues and human foods are generally so small that little is known of their metabolism and nutritional origin. They are mentioned here because future research may show that they have unexpected practical implications in the management of human diets or in the investigation of disease processes. For further details of the chemistry of carbohydrates, the reader should consult a standard textbook (Pigman, 1957).

DIGESTION AND ABSORPTION OF CARBOHYDRATES

The first stage in the digestion of foods takes place in the mouth. Chewing breaks up the structure of vegetable foods and exposes their sugars and starch to the subsequent action of the digestive juices. Many vegetable foods, if not properly chewed, fail to be digested and may cause intestinal flatulence and colic. Unripe apples and chunks of raw turnip are familiar examples. The pith of oranges, if not divided up by chewing, may occasionally coalesce in the stomach to form a ball or *bezoar* which can cause intestinal obstruction. This tendency to form bezoars is due to the high content of indigestible jelly-forming pectin found in orange pith. The same tendency is shown by the American persimmon, another fruit particularly rich in pectin.

The digestion of starch begins almost at once, since the saliva contains ptyalin, a starch-splitting enzyme. This enzyme works best in a neutral medium and is inactive in the presence of acids. Its contribution to the digestion of starch is therefore limited by the time that the acid gastric juice takes to penetrate the bolus of food entering the stomach. The acidity of the gastric contents may cause a little hydrolysis of sucrose.

The digestion of carbohydrates is chiefly accomplished in the small intestine where they are subjected to a variety of enzymes; amylase (diastase, starch-splitting) is secreted in the pancreatic juice; the small intestine itself secretes invertase (sucrose-splitting), maltase and lactase. The optimum *p*H for these enzymes is slightly on the alkaline side of neutrality, so that their action is aided by the alkaline digestive secretions of the small intestine (succus entericus) and pancreas which neutralise the acid gastric juice mixed with the food. Ultimately the starch, glycogen and dextrins of the food are all broken down to their component disaccharides and monosaccharides. Cellulose and other polysaccharides are resistant to human enzymic digestion and so pass on to the large intestine where they contribute to the bulk of the fæces, together with some fibrous tissue from meats, bacteria and the desquamated cells that are shed from the internal surface of the bowel. When, for a variety of pathological reasons, food passes with abnormal rapidity into the large bowel, it often contains some unabsorbed sugars. These are fermented by the bacterial flora with the production of carbon dioxide, methane and other gases which cause flatulence.

The hexose sugars that are either eaten as such or liberated by digestion are normally absorbed through the walls of the small intestine. Their absorption takes place at a rate faster than could be accounted for by simple physical diffusion and also against a concentration gradient, at least in the case of glucose and galactose. Energy is needed for the process. At one time it was widely held that this was provided by reactions involving the formation of hexose phosphate in the cells of the intestinal mucosa. There are difficulties in accepting this view and an alternative hypothesis is that sugar absorption may be coupled with a second and different energy-dependent transport system, such as the transport of sodium ions (Crane, 1960).

The rate of absorption is different for each of the three principal hexose sugars. Groen (1937) studied this in normal people by introducing a rubber tube into the jejunum. The tube had two rubber balloons attached to it, 50 cm. apart. These balloons could be inflated so that a length of jejunum could be blocked off. A solution of sugar was then introduced into the intestine between the balloons, and a sample of the solution withdrawn at intervals to measure the rate at which the sugar was taken up by the intestinal wall. He found that with sugar solutions of 10 per cent. or more, a 50 cm. length of jejunum absorbed in one hour 9·5 g. galactose, 8 g. glucose, but only 5 g. fructose.

Recently Dahlquist and Borgström (1961) have published experiments on man, in which the intestinal contents were collected by intubation after various test meals. Hydrolysis of disaccharides to monosaccharides appeared to take place to only a limited extent within the intestinal lumen, and it was concluded that most of the carbohydrate was absorbed as disaccharides. These may be hydrolysed subsequently within the gut wall by intracellular enzymes.

THE DESTINY OF CARBOHYDRATES IN THE BODY

The hexose sugars, once absorbed from the intestine, pass in the portal vein to the liver. Thereafter their future differs; whereas the greater part of the glucose passes straight through the liver into the general circulation of the blood, fructose and galactose are selectively taken up by the liver, so that under normal circumstances only small amounts of either escape into the general circulation. However, if the liver is damaged, its power of immediately accepting fructose and galactose from the gut is impaired. The consequent abnormal increase in the concentration of these sugars in the blood (and sometimes urine) following a test dose by mouth, is the basis of two tests of liver function—the fructose (Stewart *et al.*, 1938) and galactose (Maclagan, 1940) tolerance tests. The fructose and galactose which the liver takes up are converted to glycogen. When, eventually, this glycogen is broken down it is liberated into the blood entirely as glucose. In other words, the liver converts fructose and galactose, through the intermediary of glycogen, into glucose in the blood.

The level of glucose in the blood is regulated by a number of finely adjusted mechanisms as discussed in the next section. In order clearly to understand these mechanisms, it is useful first to consider what happens to the glucose after it leaves the blood and enters the tissues.

Glycogen and muscles

The skeletal muscles, both because of their bulk and constant activity, are the principal site in the body for the conversion of chemical energy into mechanical and thermal energy. The mechanisms by which this energy is released are described in Chapter 9. For the moment it is sufficient to say that the fuel most readily available in the muscles is glycogen. Some energy is rapidly released by the breakdown of glycogen to lactic acid. This reaction is anaerobic : *i.e.* it involves no use of oxygen. But, given a sufficient supply of oxygen, the lactate thus formed is immediately oxidised, releasing further energy. If, however, the supply of oxygen to the muscle is temporarily insufficient, some of the accumulated lactate leaks out of the cells into the blood and so finds its way to the liver. The liver is able to convert this lactate back to glycogen. The sequence : liver glycogen→blood glucose→muscle glycogen→blood lactate→liver glycogen (as illustrated in Fig. 4, 4) is generally known as the Cori Cycle, after the distinguished Nobel prizewinners, Dr C. and Mrs G. Cori of St Louis, U.S.A., who first described it.

The accumulation of lactate through temporary shortage of oxygen in the muscles begins with moderate muscular effort such as walking at about 4 m.p.h. After severe exercise it may reach 100 mg./100 ml. in the blood. Excess of lactic acid in the muscles of a quarter-mile runner may explain why they are sometimes taut and tender after a race. The same sensation only more painful may be felt by a patient with partially occluded arteries in the legs, who, through an insufficient blood supply, begins to accumulate excess lactate in his muscles even after walking a short distance. The resulting symptom is known as *intermittent claudication.* The same symptom also occurs in thiamine deficiency, since thiamine is necessary for the oxidative removal of lactate in the muscles (p. 224).

THE CORI CYCLE AND OTHER METABOLIC PATHWAYS FOLLOWED BY INGESTED CARBOHYDRATE

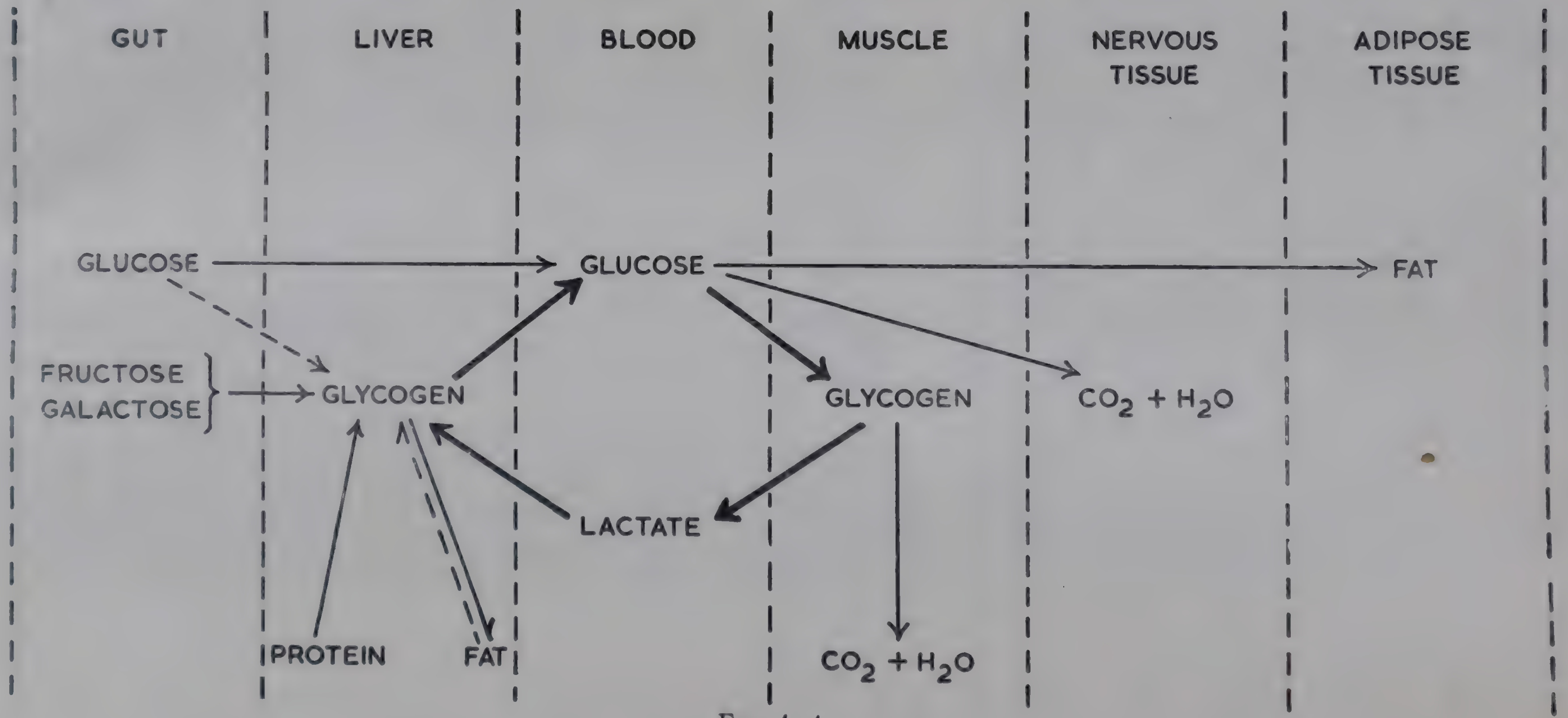


FIG. 4, 4

Glucose and the nervous system

Mental effort involves no measurable extra expenditure of energy, yet the nervous system as a whole uses considerable amounts of energy to maintain its mechanism in working order. Nearly one-fifth of the total basal metabolism takes place in the brain. Nervous tissue appears to derive its energy entirely from carbohydrate, since its R.Q. has always been found to be about 1·0 (Lambertsen *et al.*, 1953). Nerve cells oxidise glucose, which they obtain directly from the blood, with the production of carbon dioxide and water. They seem to be able to do this without glycogen as an intermediary. Although small amounts of glycogen are constantly present in nervous tissue, it is not apparently used as fuel and remains fixed in amount, even when there is an obvious shortage of glucose as evidenced by neurological symptoms and a low blood sugar. Nervous tissue seems to have no important store or reserve of energy and is therefore immediately dependent on the level of glucose in the blood for its continued activity. Perhaps this explains why the blood sugar is regulated with such precision. If the level of glucose in the blood is suddenly reduced, as for instance by the injection of excessive amounts of insulin, changes in nervous activity quickly follow. Mental confusion is a frequent symptom of insulin overdosage in diabetic patients, which may even result in hypoglycæmic coma (Chapter 42). Some psychiatrists have deliberately made use of insulin shock in the hope of permanently reducing the activity of areas in the frontal lobes of the brain in patients suffering from some forms of mental disease.

Glucose and the kidneys

The whole of the blood passes many times through the kidneys each day. In this process, glucose escapes into the glomerular filtrate but is rapidly reabsorbed by the tubules, so that only minute traces of glucose normally escape into the urine in amounts insufficient to be detected by Benedict's or Fehling's test. If, however, the level in the blood is unduly high, the tubules are overloaded and the renal threshold is exceeded, with consequent glycosuria.

Storage of carbohydrate

1. **As glycogen.**—The body's stores of glycogen are small. This is amplified in Table 4, 1, adapted from Soskin and Levine (1952).

TABLE 4, 1. *Carbohydrate content of a normal man*

Body weight	65·0 kg.
Liver weight	1·8 kg.
Muscle weight	36·0 kg.
Extracellular fluid volume	15·0 *l.*

TABLE 4, 1. *Carbohydrate content of a normal man*—contd.

	Per cent.	g.
Muscle glycogen	0·7	250
Liver glycogen	6·0	110
Extracellular glucose	0·1	15
Total carbohydrate		375
Caloric value		1500 Cal.

2. **As fat.**—Whenever the diet provides more glucose than the tissues are immediately able to accept, the excess is turned into fat and deposited in the adipose tissues of the body. This was first clearly demonstrated by the classical experiment carried out over a hundred years ago by Sir John Bennet Lawes and Sir Joseph Gilbert (1853) at Rothamsted. They showed that young pigs put on four times more fat than their diet supplied, and concluded that fat is formed from starch within the body. At one time it was thought that this conversion of blood sugar into fat takes place entirely in the liver. Undoubtedly the liver is in part responsible, but the conversion also takes place in the adipose tissue itself (Wertheimer & Shapiro, 1948).

The fuel of muscle.—The above account of the disposal of the carbohydrates is classical orthodox physiology. Implicit in it is the opinion, often quoted in textbooks, that carbohydrate is the ' prime fuel ' of the body. This view was first questioned as a result of the experiments of Stetton and Boxer (1944). Using deuterium as an indicator, they showed that in rats on a high carbohydrate diet at least ten times as much glucose was synthesised into fatty acids as into glycogen. Further isotopic studies have shown that the rate of turnover of glucose in the body is much slower than the rate of turnover of the non-esterified fatty acids (NEFA). Dole (1958) has calculated that NEFA can provide energy for the tissues at a rate two and a half times as fast as can glucose. Although the various routes for the disposal of the blood glucose indicated in the figure on page 56 are certainly all available and are all utilised, it is probable that NEFA rather than glucose is the ' prime fuel ' of the body.

THE REGULATION OF THE LEVEL OF GLUCOSE IN THE BLOOD

Having now considered the possible fates of carbohydrates in the body, it is appropriate to return to the regulation of the common pathway, namely the glucose in the blood, by which they are distributed to the tissues. The blood before breakfast usually contains 80 to 100 mg. glucose/100 ml. After a meal the level rises because, as already explained, the glucose absorbed from the gut passes through the liver into the general circulation ; it may reach 130 mg./100 ml. or even more, but rarely exceeds 180 mg./100 ml., at which point glucose usually overspills into the urine. Thereafter the blood level rapidly declines as a result of the passage of glucose into the tissues. Part is taken up by the nervous and perhaps glandular tissues and used at once as a source of energy. Part is taken up by adipose tissue and converted into fat. A further part may be accepted by the muscles and converted to glycogen, though the extent to which this happens depends on the reserves of glycogen already there. It has already been said that the muscles usually contain a total of about 250 g. of glycogen ; their ability to increase stores beyond this amount is limited.

On the other hand, when the body is fasting and receiving no glucose from the gut, the brain and to some extent other tissues will continue to draw on blood glucose for their needs, but this does not necessarily result in any serious reduction in the blood glucose level because of certain compensatory mechanisms. The liver is able to release more glucose into the blood from its store of glycogen. But the glycogen store of the liver is small and usually does not exceed 100 g. When this store is depleted the liver then begins to make new glycogen from other sources, notably from straight-chain amino acids derived from protein. The more complex amino acids are relatively less useful for this purpose. This partial conversion of protein to glycogen in the liver is known as *gluconeogenesis*. As to whether fats can also contribute to gluconeogenesis has been much disputed. It seems probable however that small fragments of metabolised fatty acids can be built back into carbohydrate via the metabolic pool (Chapter 9) : also the glycerol, which comprises about 10 per cent. of all neutral fats, is readily converted to glycogen.

The surprising fact is that even in the last stages of starvation a sufficient level of glucose is maintained in the blood, so that the intellectual faculties and other activities of the nervous system survive (Chapter 26). This is achieved by the twofold mechanisms of continued gluconeogenesis in the liver and the sparing use of carbohydrate by the muscles. How readily fats can be used to spare carbohydrate is shown by the fall in R.Q. that occurs in normal people only a few hours after a meal, especially if exercise has been taken.

Hormonal control

The pathways by which glucose enters and leaves the blood are controlled by a variety of hormones.

1. **Insulin** is a protein secreted into the blood by the beta cells in the islets of Langerhans of the pancreas. The normal stimulus to insulin secretion is the ingestion of carbohydrates. The injection of insulin (extracted from the pancreas of animals) results in a *rapid* fall in blood glucose due to the passage of glucose into the cells of muscles and other tissues. Although insulin has been studied for over 40 years, the chemical nature of the mechanism whereby it facilitates the passage of glucose out

of the blood and into the cells remains an elusive mystery. There is an enormous literature on this subject, which is at the heart of many biochemical and medical problems. As an introduction, a small monograph by Krahl (1961) and the proceedings of a symposium organised by the British Insulin Manufacturers (Young *et al.*, 1960) can be strongly recommended.

2. **Adrenaline** is one of the hormones produced by the adrenal *medulla* ; its injection produces a *rapid* and transitory rise in blood glucose by releasing glucose from the stores of glycogen in the liver. The speed with which adrenaline achieves this makes it a valuable aid in overcoming the effects of insulin when this is inadvertently given in excessive dosage to diabetic patients.

In addition the following three hormones can also produce a rise in blood sugar.

3. **Glucagon.**—This is the name given to a hormone that has not yet been isolated but has been shown to be present in extracts of pancreas, duodenum and other tissues. It is produced by the alpha cells of the pancreatic islets and perhaps by the mucosa of the upper gastrointestinal tract. The rise in blood sugar produced by glucagon is probably achieved by the breakdown of liver glycogen. In this way glucagon may actually assist the physiological action of insulin by providing more glucose in the blood for deposition in the muscles.

4. **Cortisone** and hormones allied to it are produced by the *cortex* of the adrenal glands. In contrast to insulin and adrenaline, their effect is slow and prolonged. Repeated injections of cortisone sometimes result in a sustained elevation of blood sugar. The chief cause of this seems to be an increase in the formation of new liver glycogen (gluconeogenesis) from protein and fat and hence to a greater potential supply of blood glucose.

5. **The growth hormone of the anterior pituitary.**—This promotes the growth of young animals and, when injected into adult animals, sometimes produces a sustained elevation of blood glucose probably by opposing the action of insulin and preventing the entry of glucose into the tissues. Since the growth hormone has only lately been isolated in pure form, it is still uncertain whether it is identical with the anti-insulin factor ; however, the association is certainly very close.

There remains the question of *insulinase*—the proteolytic enzyme which selectively destroys and inactivates insulin released from the pancreas. Insulin injected into the body exerts its effect for a few hours only, presumably because of the activity of this enzyme. But the factors that control this activity are not yet known.

These various regulatory mechanisms summarised in simple form in Fig. 4, 5 are normally so precisely balanced that the blood glucose is held at a level that varies within restricted limits (60 to 180 mg./100 ml.) so that the supply of glucose to the brain and other tissues is steadily maintained.

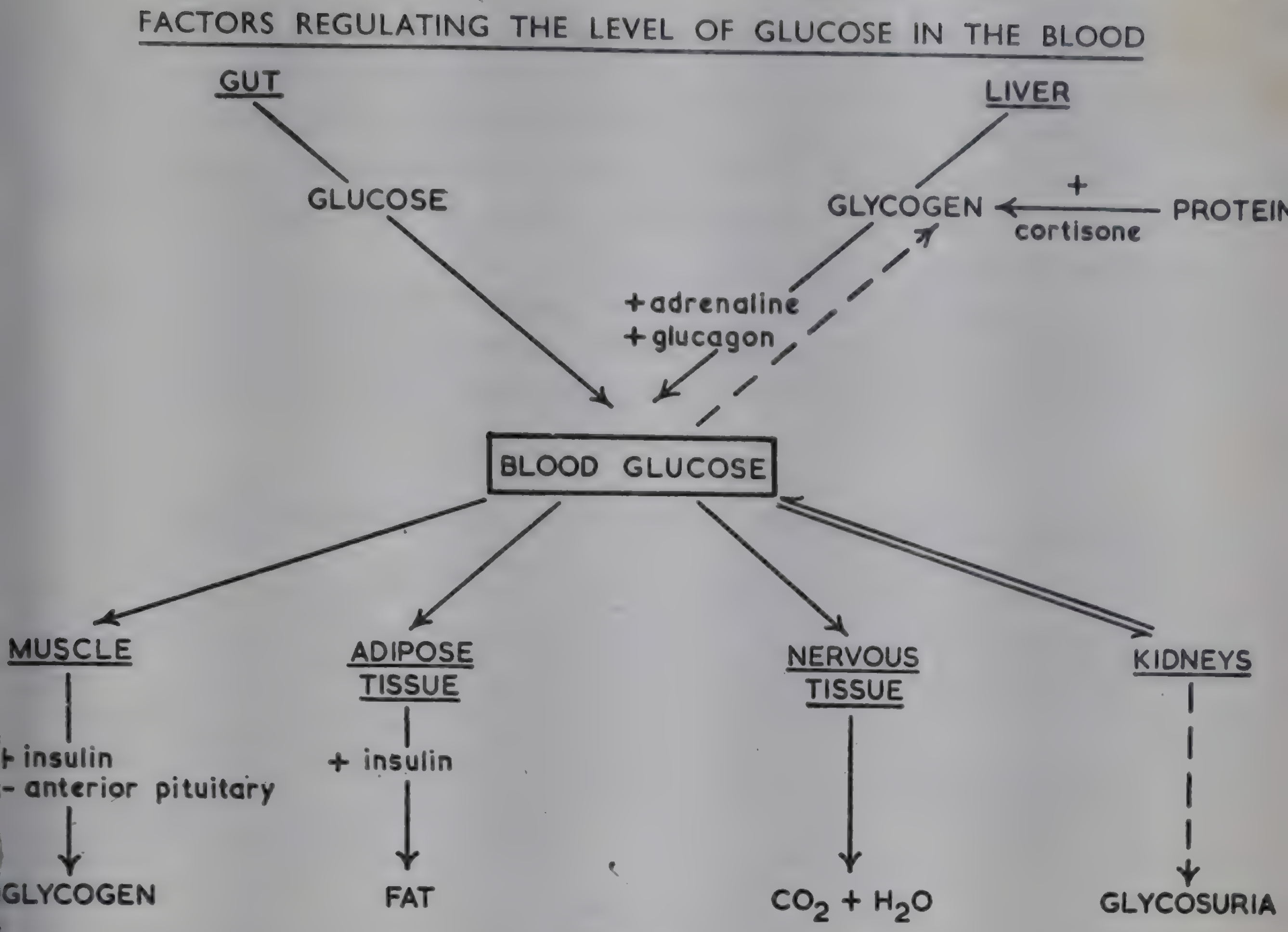


Fig. 4, 5

Hypoglycæmia

If the blood glucose falls below normal levels neurological and other symptoms result. This is called hypoglycæmia. It sometimes occurs in healthy people some hours after a meal rich in carbohydrates, especially following muscular exertion, perhaps because of an excessive release of insulin. It is also a feature of several pathological conditions—notably Addison's disease which is due to destruction of the adrenal glands. The lack of adrenal hormones, both cortical and medullary, renders the patient with Addison's disease extremely sensitive to insulin, so that even a few units of insulin, either injected or from the patient's own pancreas, may cause profound hypoglycæmia.

Hyperglycæmia

This may be defined as an elevation of blood glucose above the normal upper limit which is generally taken as 180 mg./100 ml., the level at which glucose usually begins to appear in the urine. Sustained hyperglycæmia accompanies the clinical syndrome of diabetes mellitus. The immediate cause of diabetes is an absolute or relative failure in the secretion of insulin by the pancreas. Absolute failure results when the pancreas is removed surgically.

Homœostasis

Fortunately for most normal people the various factors that tend to cause hypoglycæmia on the one hand and hyperglycæmia on the other are so finely adjusted that neither state occurs. This is a beautiful example of the principle of homœostasis (as first expounded by Walter Cannon) whereby the body's internal environment (conceived by Claud Bernard) is precisely maintained within narrow, normal limits despite wide fluctuations in external circumstances, which in this case include food intake and exercise.

Glucose tolerance test.—From a practical standpoint, the integrity of the normal homœostatic mechanisms that regulate the blood glucose can be simply demonstrated by means of this test, described in Chapter 42.

THE PROTEIN-SPARING ACTION OF CARBOHYDRATES

As explained in the previous section, the liver utilises protein for gluconeogenesis to replenish its stores of glycogen whenever these become depleted by prolonged fasting or lack of carbohydrates in the diet. This use of protein is wasteful, both for physiological and economic reasons. First, the destruction of a protein and the conversion of a part of its amino acids into glycogen is a process that, on balance, uses more energy than it liberates. Hence energy derived in this way from protein is relatively less efficient than the direct combustion of carbohydrates ingested as such. Secondly, most foods rich in protein are considerably more expensive than foods rich in carbohydrate.

In dietetic practice it is desirable that the food should contain sufficient carbohydrate to spare the wasteful use of dietary protein merely as a source of energy, and enable it to be used to best advantage—for maintaining the nitrogenous structures of the body. There is good evidence that if dietary protein is to be used in the most economical way, it should always be accompanied by carbohydrate in the same meal (Cuthbertson & Munro, 1939). Hence the usual dietary combinations of bread and cheese, rice and curried meat, fish and chips, roast beef and Yorkshire pudding are not only hallowed by tradition, but based on sound physiological principles.

THE VALUE OF CARBOHYDRATE IN THE DIET

The Arctic explorer Stefansson and a colleague lived for a whole year on a diet composed only of meat (McClellan & Du Bois, 1930) and so almost devoid of carbohydrate. They kept in good health. Members of some meat-eating tribes get little or no carbohydrate in their diet and it does not seem as if carbrohydrate is a dietary essential—at least for adult man.

Nevertheless from necessity most men are at least partial vegetarians and so carbohydrates are a major component of their diets. In prosperous industrial communities more and more fat appears to be chosen in the diet and this restricts the intake of carbohydrates. The view is widely held that these diets with a high proportion of fat contribute to degenerative diseases, especially of the arteries. This is discussed in Chapter 40. It is certain that a higher proportion of carbohydrates could be eaten by men and women in Western Europe and North America than is customary, with no disadvantage to health.

Carbohydrate is useful in supplying energy and from this standpoint it does not matter whether it is provided by starch from potatoes, wheat or rice, sucrose from sugar beet, fructose from honey or glucose from the industrial chemist. It is the quantity rather than the quality that is important : although from the economic standpoint, natural starch is usually the cheapest source.

There can be no doubt that the biological success of man in surviving and multiplying on the earth has been largely due to his ability to cultivate concentrated sources of vegetable carbohydrate ; but here a word of caution is necessary. There is a current tendency to think of the cereals, fruits and roots as providing only carbohydrates. In fact, the cereal grains and particularly the pulses (peas and beans) are also important and in some countries even vital sources of protein and of minerals and vitamins, as explained in the next chapter.

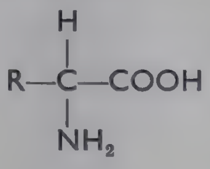
CHAPTER 5

PROTEINS

IN Chapter 2 it was explained that dietary proteins are a source of energy in the body, but in this respect they are normally less important than either carbohydrates or fats. The contribution made by proteins to the caloric value of most well-balanced diets is usually between 12 and 15 per cent. of the total and seldom exceeds 20 per cent. Their real importance lies in the fact that every cell in the body is partly composed of proteins which are constantly subject to wear and replacement. Carbohydrates and fats contain no nitrogen or sulphur, two essential elements in all cellular proteins. Whereas the fat in the body can be derived from dietary carbohydrates and the carbohydrates from proteins, the proteins of the body are inevitably dependent for their formation and maintenance on the proteins in food.

CHEMISTRY

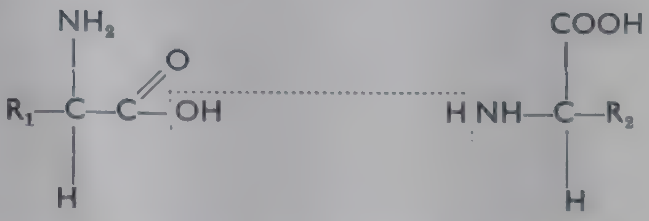
Proteins consist of very large molecules with molecular weights between 17,400 and 900,000. In their native state some are soluble and some insoluble in water. They can be broken down by hydrolysis into simple units—the amino acids. These are all characterised by the presence of a carboxyl (COOH) group with acidic properties and an amino (NH_2) group with basic properties, attached to the same carbon atom. The rest of the molecule varies with the particular amino acid ; the structure of an amino acid may be represented by the formula :



$$\mathrm{R-\underset{NH_2}{\overset{H}{C}}-COOH}$$

where R represents the remainder of the molecule. It would be reasonable to expect that an infinite variety of compounds of this composition might exist in nature ; but in fact only twenty-three amino acids have so far been identified in biological materials.

The amino acids are linked together in the protein molecule by the peptide linkage :



$$\mathrm{R_1-\underset{H}{\overset{NH_2}{C}}-\overset{O}{\overset{\|}{C}}-OH \quad \cdots\cdots\cdots \quad H\,NH-\underset{H}{\overset{COOH}{C}}-R_2}$$

The basic (amino) group of one amino acid is linked to the acidic (carboxyl) group of another, with the elimination of a molecule of water.

Since any two amino acids can be joined to form two different peptides by this linkage, and since every amino acid may occur in varying amounts in different proteins, it is obvious that the possible number of proteins which may exist in nature is almost infinite. Every species of animal has its characteristic proteins—the proteins of beef muscle, for instance, differ from those of pork muscle. It is the proteins that give each species its specific genetic and immunological characters and also determine many of the differences between individuals within a species.

The sources and nature of proteins

Much of the protein in human food comes directly from cellular tissues, both of plant and animal origin. Comparatively little is known of the chemical structure of *cellular proteins* since they undergo inevitable alterations when the cell is broken down in the process of their extraction. Nevertheless it is safe to guess that they disperse readily in water and are easily digested, once released from the cell membranes that enclose them. Foodstuffs also contain a variety of *extracellular proteins*, the nature of which is much better understood since they can be studied more easily in their native state by X-ray analysis and other methods. Animal proteins can be divided broadly into two classes—fibrous and globular.

Fibrous proteins.—These consist of long coiled or folded chains of amino acids bound together by peptide linkages. They are found in the protective and supportive tissues of animals such as skin, hair, feathers, tendons and the fins and scales of fish. The fibrous proteins in such tissues are very insoluble in water and for the most part indigestible. Nevertheless they are a valuable by-product of the food industry since gelatin and other nitrogenous substances can be extracted from them. *Keratin*, the chief protein of hair, has been much studied by the wool industry. It is interesting chemically because it contains 11 per cent. of the sulphur-containing amino acid, cystine. Its practical importance lies in its resistance to solution and its *elasticity*. The latter property is common to all the fibrous proteins. Their contracted molecules can be stretched out straight and, under suitable conditions, will remain stretched ; this is the secret of a ' permanent wave ' in the hair. Other fibrous proteins include the *collagen* of connective tissue, the *fibrin* of a blood clot and the *myosin* of muscle. The latter is an intracellular protein. All of these three consist of long, elastic, molecular chains and although insoluble in water are more digestible than keratin. The Chinese have long known how to extract nourishment out of shark fins and other unpromising sources of fibrous proteins. The prudent housewife with a good stock pot, and particularly with the aid of a pressure-cooker, can do the same.

Globular proteins.—These are found in the extracellular fluids of animals and plants in which they readily disperse, either in true solution or colloidal suspension. The most important from the standpoint of nutrition are : *caseinogen* in milk, *albumin* in blood plasma and egg white and the plasma *globulins*. The exact configuration of their rounded molecules is a challenge to biochemists. For the nutritionist it is sufficien to know that they are not only easily digestible but also contain in thei structure a good proportion of the essential amino acids ; so they are some of the best of nutrients.

Glutelins and prolamines.—These are the chief plant proteins. Glutelins, which are insoluble in neutral solutions, but soluble in weak acids and alkali, are present in cereals. They include glutenin from wheat, hordenin from barley and oryzenin from rice. These are probably not homogenous substances. Prolamines are insoluble in water but dissolve in alcoholic solution. On hydrolysis they give large quantities of proline and ammonia. Typical prolamines are gliadin from wheat and rye, zein from maize and hordenin from barley.

Gluten is a mixture of gliadin and glutelin which gives wheat a unique position as a human food. Gluten has a stickiness which enables the molecules, present in wheat flour, to be bound together under the influence of moderate heat with the production of dough, from which bread is baked. Rye has a small content of gluten and so (with difficulty) can be made into a loaf. Oats, barley, maize, millets and rice cannot be made into bread. The grains may be eaten after boiling or their flour made into porridge, bannocks, tortillas, etc.

Protamines and histones.—These are simple polypeptides with molecular weights of only 2000 to 4000. They are found in male fish roes and also in cellular nucleoproteins. Protamines have a practical use in the commercial production of delayed-action insulins.

Coagulation and denaturation

When water-soluble proteins are subjected to heat at about 100° C. or above, as in the normal process of cooking, they *coagulate*. The change of the white of an egg on boiling is a familiar example. Once a protein has undergone this change its properties are permanently altered ; it can never be brought back into simple solution in water and its specific properties, *e.g.* enzymic, hormonal or immunological, are permanently destroyed. Proteins also undergo a lesser change, known as *denaturation*, in which they become less soluble in water. This occurs when they are exposed to a variety of physical agents such as moderate heat, ultraviolet light, alcohol and mild acids or alkalis. The exact nature of the denaturation process is obscure ; it apparently involves some disorganisation of the specific arrangement of the component amino acids. To a certain extent it is reversible, once normal conditions are restored ; but most enzymes and allergens lose their specific properties when once denatured. Proteins are most easily denatured at their iso-electric point, *i.e.* the particular *p*H at which the electric charges on their NH_2 and COOH groups precisely balance ; this varies from one protein to another. It seems probable that many of the finer arts of cooking, such as simmering, the addition of vinegar, lye or wine, depend for their success on securing the proper degree of denaturation in preparation for the final coagulation ; but the wedding of the science to the art of nutrition is slow, and those who know the secrets of the latter are sometimes reluctant to reveal them. Fortunately for humanity at large, neither coagulation nor denaturation seem to affect the digestibility of dietary proteins. A hard-boiled egg is just as nourishing as a raw egg for a normal man.

THE ESSENTIAL AMINO ACIDS

Plants can synthesise all the amino acids they need from simple inorganic chemical compounds, but animals are unable to do this because they cannot synthesise the amino (NH_2) group ; so in order to obtain the amino acids necessary for building protein they must eat plants, or other animals which have in their turn lived on plants.

The human body has certain limited powers of converting one amino acid into another. This is achieved in the liver, at least partly by the process of *transamination*, whereby an amino group is shifted from one molecule across to another under the influence of an enzyme, transaminase, the coenzyme of which is pyridoxal phosphate (Chapter 14). However, the ability of the body to convert one amino acid into another is restricted. There are several amino acids which the body cannot make for itself in sufficient quantities from other products of the metabolic pool in order to satisfy normal needs, and so must obtain them from the diet. These are termed *essential amino acids*.

The adult human body can maintain nitrogenous equilibrium on a mixture of eight pure amino acids as its sole source of nitrogen. These eight are : isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. To maintain growth in infants, histidine and perhaps argenine are also needed. Fig. 5, 1 gives the structural formulæ of the principal amino acids.

Individual Characteristics of Amino Acids

The chief importance of the amino acids lies in the fact that they are the building-stones of the tissue proteins. Nevertheless several of them are known to have additional and individual physiological properties which deserve brief mention.

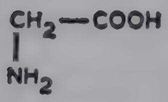
Glycine—the simplest amino acid—is utilised by the liver in the elimination of toxic phenols. For instance, benzoic acid, when taken by mouth, is conjugated with glycine in the liver and excreted as hippuric acid in the urine. During periods of rapid growth the demand for glycine may be enormous. For the young chick, glycine is an essential amino acid since its supply becomes, for a time, a limiting factor to growth.

Glutamic acid.—This dicarboxylic acid easily loses its amino group to keto acids such as pyruvic acid under the influence of the enzyme transaminase, in this way giving rise to other amino acids in the body. Glutamic acid is the predominant amino acid in wheat protein (gliadin).

The principal amino acids

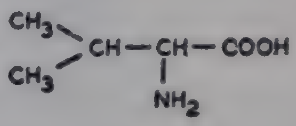
A. Aliphatic amino acids

1. Monoamino-monocarboxylic acids

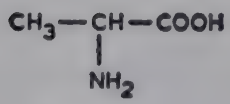


$\underset{NH_2}{CH_2}-COOH$

Glycine

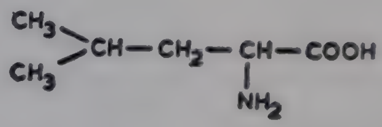


Valine

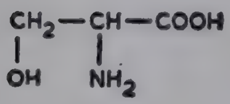


$CH_3-\underset{NH_2}{CH}-COOH$

Alanine

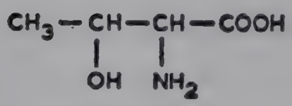


Leucine



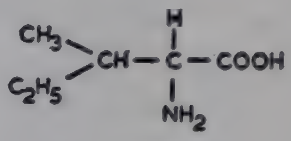
$\underset{OH}{CH_2}-\underset{NH_2}{CH}-COOH$

Serine



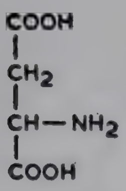
$CH_3-\underset{OH}{CH}-\underset{NH_2}{CH}-COOH$

Threonine

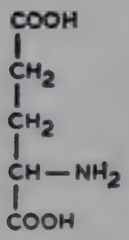


Isoleucine

2. Monoamino-dicarboxylic acids

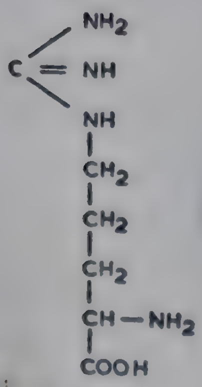


Aspartic acid

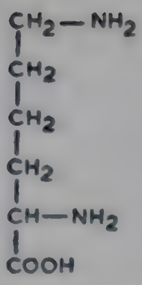


Glutamic acid

3. Diamino-monocarboxylic acids



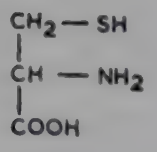
Arginine



Lysine

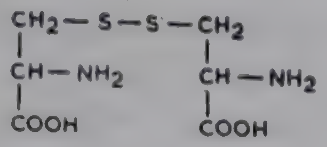
FIG. 5, 1

4. *Sulphur-containing amino acids*



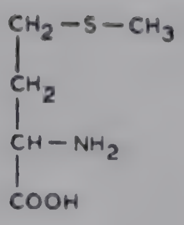
$$CH_2{-}SH \cdot CH{-}NH_2 \cdot COOH$$

Cysteine



$$CH_2{-}S{-}S{-}CH_2 \;\; (CH{-}NH_2)_2 \;\; (COOH)_2$$

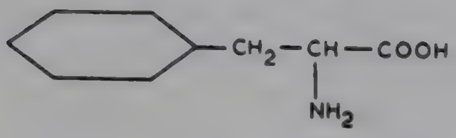
Cystine (dicysteine)



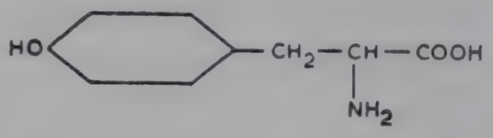
$$CH_2{-}S{-}CH_3 \cdot CH_2 \cdot CH{-}NH_2 \cdot COOH$$

Methionine

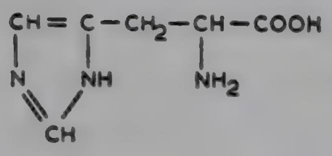
B. Aromatic and heterocyclic amino acids



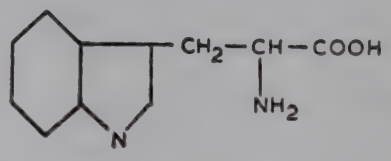
Phenylalanine



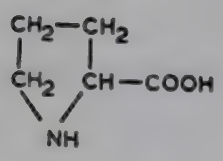
Tyrosine



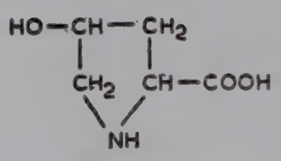
Histidine



Tryptophan



Proline *



Hydroxy-proline *

* Both proline and hydroxy-proline have *potential* amino groups.

FIG. 5, 1 (*continued*)

In purified form its strong, meaty flavour gives it commercial value as a flavouring agent for cooking.

Arginine is concerned with the formation of urea in the liver, by the process known as the ornithine-arginine cycle, first proposed by Krebs. The reader is referred to textbooks of biochemistry for details of this process.

Lysine is deficient in most vegetable seed proteins with the exception of pulses (peas and beans). Furthermore it does not exchange its amino group with other acids in the body, as Schoenheimer (1942) originally showed with the use of ^{15}N-labelled amino acids. **Threonine** is apparently the only other essential amino acid of which this is true. In other words lysine and threonine each form ' a single indispensable chemical unit which has to be supplied as such to the animal ' (Schoenheimer, 1942). Of all the amino acids, lysine is the most likely to be deficient in poor vegetarian diets.

Cysteine, cystine and methionine, are the principal sources of sulphur in the diet of man. The body can make cysteine and cystine from methionine but not *vice versa*, so that methionine is the dietary essential. Cysteine is present in the body partly in its double S-S form—cystine (Fig. 5, 1)—as for instance in the keratin of hair and in insulin, in each of which it represents about 12 per cent. of the whole protein molecule.

Methionine is also concerned with the important physiological process of *transmethylation*. For some unknown reason the mammalian body easily becomes deficient of methyl (CH_3) groups for the synthesis of choline (Chapter 6) which contains three such groups in each molecule. The chief dietary source of methyl groups appears to be methionine and betaine ($(CH_3)_3.N.CH_2.COOH$) which accordingly are called *methyl donors*. Methionine gives up the terminal CH_3 group attached to its sulphur atom. Dietary deficiency of methionine in rats results in a fatty liver which can be cured by restoring this amino acid to the diet, or alternatively, by giving the choline which the body would normally form from it.

Phenylalanine and tyrosine.—These two amino acids which contain a benzene ring in their molecules provide the raw material from which the body makes the hormones adrenaline and thyroxine. They are also the origin of the pigment *melanin* which occurs in the hair, the choroid lining of the eye and in the skin. The pigmentation of the skin in Addison's disease is the result of melanin deposition and is supposed to reflect the failure of the adrenal glands to make adrenaline, with consequent diversion of phenylalanine and tyrosine to melanin formation. The body can convert phenylalanine to tyrosine, but not *vice versa*, so that the former is the dietary essential.

Histidine.—This amino acid is apparently essential for growth and possibly for repair of human tissues because the body is unable to make the basic ring structure of its molecule. Once provided with this structure it can add on the amino group without difficulty. By losing its carboxyl (COOH) group, histidine is converted to histamine, an important physiological substance which is normally freely present in the lumen of the intestine and (in bound form) in basophil leucocytes and in many tissues. The release of histamine into the skin accounts for urticaria (nettle-rash) such as may result from food allergy. Histamine stimulates the secretion of hydrochloric acid by the stomach and is used for this purpose in tests of gastric function.

Tryptophan is the raw material from which some synthesis of nicotinic acid undoubtedly takes place in the body (p. 229). It is also the precursor of 5-hydroxy-tryptamine (5 HT), a physiological substance which causes vasoconstriction. It is present in many tissues, especially the argentiffin cells of the intestinal mucosa, and in the blood platelets. When the platelets break up in the formation of a blood clot, they release 5 HT which appears to prevent bleeding by causing vasoconstriction of the neighbouring blood-vessels.

Proline and hydroxyproline consist essentially of a pyrrole ring. This same ring structure is found in the porphyrins which go to make hæmoglobin and the cytochromes. The porphyrin molecule, and also that of cyanocobalamin (Chapter 14), contain four pyrrole rings. It seems likely, though not proved, that these pyrroles originate from the prolines in food.

DIGESTION

Proteins undergo hydrolysis in the gastrointestinal tract, resulting in the release of amino acids. This is accomplished by the action of three proteolytic enzymes discussed in the following paragraphs.

1. **Pepsin.**—This enzyme is secreted by the peptic cells of the mucosa of the stomach. It works best in an acid medium (optimum *p*H about 1·2) which is normally provided by the hydrochloric acid secreted by the oxyntic cells of the gastric mucosa. Pepsin breaks down proteins to smaller units, polypeptides, also composed of amino acids bound together by the peptide linkage. No free amino acids are liberated by gastric digestion. The initial partial digestion of proteins in the stomach is not essential to secure their ultimate absorption.

Rennin is another proteolytic enzyme secreted by the stomach of newborn mammals. It clots the protein of milk (caseinogen) and is the active principle of *rennet*, an extract from the stomach of animals or from certain plants used to curdle milk. There is no evidence, however, that rennin plays any part in protein digestion in the adult.

2. **Trypsin.**—This is the chief proteolytic enzyme of the pancreatic juice. It acts best in an alkaline medium (optimum *p*H about 8) and converts proteins into polypeptides. The pancreatic juice also contains other protein-splitting enzymes and there can be no doubt that it is the principal means whereby proteins are normally digested. When disease of the pancreas obstructs or prevents the flow of the juice, failure of protein digestion is shown by the presence of undigested fibres of meat in the stools and by an increase in the amount of fæcal organic nitrogen. At the same time the stools and flatus are foul-smelling, due to the action of bacteria in the large intestine on undigested protein, producing hydrogen sulphide and other products of putrefaction. The same is often true when protein absorption is impaired by too rapid passage of the food through the small intestine.

3. **Erepsin.**—This is the name given to the mixture of proteolytic enzymes present in the succus entericus—the juice that exudes from the mucosa of the small intestine. Sir Howard Florey and his colleagues (1941) considered that the proteolytic activity of this juice is due to the large number of mucosal cells that are regularly sloughed from the intestinal walls and are themselves in the process of autolysis by the action of their own proteolytic enzymes. The effect of erepsin is to complete

the hydrolysis of polypeptides and peptides to their component amino acids.

The digestion of proteins has been generally considered to proceed until, by various stages, they are completely broken down to amino acids and are thus absorbed. This view has held the field since Van Slyke and Meyer (1912) first demonstrated the rise in amino nitrogen in the blood during protein absorption. However, Fisher (1954) has advanced the alternative view that proteins may not be completely hydrolysed before they are absorbed. His chief evidence is that the absorption of protein usually takes place in less time than appears to be required by proteolytic enzymes to produce amino acids. A further argument is that a dietary protein occasionally exerts a general allergic response, such as urticaria, in people sensitive to it. At least some part of the protein must have passed unchanged through the intestinal mucosa. Simple peptides and amino acids, being common to all species of animals, have no allergic or immunological properties.

It seems likely that, in general, proteins from animal sources are more easily and rapidly absorbed than vegetable proteins ; perhaps because vegetable proteins are often enclosed in a cellulose covering. Phansalkar and Patwardhan (1955) have shown that the immediate urinary excretion of protein waste products is larger after a meal containing animal protein than when the same amount of protein is provided by vegetables.

Fæcal nitrogen.—The alimentary canal carries out the digestion and absorption of protein effectively. Less than 10 per cent. of the dietary protein usually appears as nitrogen in the fæces. Although most of the fæcal nitrogen comes from incompletely digested and absorbed foods, some is derived from the intestinal secretions and shed epithelial cells. This is the endogenous fæcal nitrogen, which can be measured by collecting the fæces from an animal during an experimental period on a diet containing no protein.

As stated in Chapter 2, Atwater concluded from his experiments that 92 per cent. of the dietary protein was digested and absorbed. Subsequent experience has shown that amongst healthy persons eating the usual ‘ civilised ’ diets there is little variation from this figure. If the diet consists of unrefined cereals and coarse vegetables, digestion may be less complete and fæcal losses of nitrogen will be higher.

DESTINY OF DIETARY PROTEINS

The products of protein digestion, once absorbed from the small intestine, pass via the portal vein to the liver, where some are metabolised and others pass into the general circulation of the blood and thus to every tissue in the body.

It is probable that the cells of each tissue make for themselves their own characteristic proteins from the products of protein digestion. The cell proteins, though containing structural material (the ‘ cyto-skeleton ’) are of particular importance because of their content of enzymes concerned with the essential metabolic processes of the cell. The *mitochondria* are centres of enzymic activity.

Some tissues actively secrete proteins. Examples are: (1) The pancreas, which not only produces the protein insulin secreted into the blood, but also the proteins amylase, trypsin and lipase secreted into the intestinal lumen, which are responsible respectively for the digestion of carbohydrates, proteins and fats. (2) Several hormones, such as those produced by the pituitary gland, and by the placenta during pregnancy, are either proteins or protein derivatives. Obviously these glands have a steady demand for the raw material from which their secretions are made, and the same applies to many other tissues with particular hormonal or enzymic activities (*e.g.* the intestinal mucosa).

There must be constant competition between the various tissues of the body for the products of protein digestion, more especially for the particular essential amino acids (p. 68) needed by each. Just how their equitable distribution is regulated is not known. It used to be thought that the plasma proteins (p. 75) were the ' common currency ' by which proteins are supplied throughout the body, but there is now indirect evidence that they cannot easily provide for the immediate needs of the tissues which normally obtain their supplies of amino acids and peptides direct from the protein of the diet.

De-amination.—After the needs of the tissues are satisfied, there may remain a surplus of ingested protein products for which the body has no immediate specific use. The amino acids not required for the needs of the tissues are taken up by the liver and there de-aminated, *i.e.* the amino (NH_2) group is removed and subsequently built up into urea, in which form it is excreted by the kidneys. The remainder of the amino acid molecule is then available, either for direct oxidation to CO_2 and water or for ultimate conversion to carbohydrate or fat.

PROTEIN STORAGE

It is often said that the body has no store of protein. This is true in the sense that there is no organ in the body that contains a static reserve of it, like glycogen in the muscles or fat in the adipose tissues. Nevertheless the normal, well-fed human body contains about 11 kg. of protein (Chapter 1), of which the body can lose about 3 kg. without serious loss of function (Chapter 26). In this sense, the store of protein in the body is actually much greater than the store of glycogen (p. 57).

Addis and his colleagues (1936) were the first to show that when rats were given a diet deficient in protein a marked loss of protein from the tissues occurred. The relative proportions are interesting; the liver could lose 40 per cent., the alimentary tract and pancreas 30 per cent., the muscles and skin 8 per cent. and the brain 5 per cent. of their original protein content. In the opposite way it has been shown by Bray (1953) and by Holmes and his colleagues (1954, 1956) that malnourished African children and adults, when fed a good diet, can retain nitrogen for weeks and yet may not show the anticipated gain in body weight. This was because of their failure to retain a corresponding amount of body water. Passmore *et al.* (1955*a*) have obtained evidence consistent with the view that the concentration of cellular protein of normal young men can be increased by simple overfeeding. Probably the protein content of the normal human cell varies by as much as 5 per cent. or even more and that at no point can it be said that an individual is well nourished by virtue of possessing some fixed and arbitrary level of cellular proteins. The level of serum albumin probably reflects roughly the level of protein in the mobile pool in the cells. This is fully discussed by Allison (1955) and by Whipple (1956).

However, a warning must be given against the idea that the human body can remain in health with only minimal amounts of protein in its cells. The work of Miller (1950) has shown how quickly depletion of protein from the liver in rats can lead to failure of at least one enzyme—xanthine oxidase. It seems certain that the liver, depleted of essential enzymes, is particularly susceptible to damage by infections or chemical toxins.

EFFECTS OF HORMONES

Male sex hormone.—Testosterone and allied substances (p. 96) when injected into man and experimental animals, in addition to their influence on sexual function, promote nitrogen retention and a positive nitrogen balance. In this way they may promote the growth of children. A variety of chemical analogues of testosterone produce this effect on nitrogen metabolism with relatively little action on the sexual organs. They are known as ' anabolic hormones ' and have a place in medicine in the treatment of chronic wasting diseases, especially during rehabilitation. Their use may also mitigate the loss of nitrogen which follows wounds, fractures and burns (p. 673).

Adrenal cortical hormones.—All these hormones (p. 96) stimulate the breakdown of protein and increase the carbohydrate content of the tissues. Their use causes increased urinary excretion of nitrogen and a depletion of protein reserves.

Growth hormone.—This pituitary hormone causes well-marked nitrogen retention both in experimental animals and in man. This is probably due to an increased rate of lipid metabolism which ' spares ' the breakdown of protein.

EFFECTS OF PROTEIN DEFICIENCY

The first effect of protein deficiency is to reduce the protein content of the cells, especially in the liver. To what extent this involves a loss of optimal cellular activity is not precisely known, but it seems reasonable to attribute the listlessness and lack of vigour of people who live on very poor diets, at least partly to insufficient enzymes. The amount of protein withdrawn from the cells under conditions of dietary deficiency depends very much on whether the diet contains enough carbohydrate to spare the protein. If the supply of calories is inadequate, the labile reserve of tissue proteins is used not only to maintain the blood sugar but also to provide a direct source of energy ; in consequence the liver, skeletal muscles and other tissues become reduced in size and the body loses weight. Even if the diet is adequate in calories, a steady exchange of tissue proteins continues and a small fraction of the amino groups released into the metabolic pool fails to be reconverted into new cellular protein. This fraction is converted to urea by the liver and excreted by the kidneys. If the diet is unable to supply sufficient amino acids to replace this inevitable loss, a state of negative nitrogen balance results, *i.e.* more nitrogen is lost in the urine than the diet supplies, the lean body mass will shrink and in consequence the weight of the body will decline. The gradual withdrawal of protein from the cells is at first sufficient to maintain a normal concentration of protein in the circulating plasma of the blood, but with increasing protein depletion the plasma proteins are affected.

The plasma proteins

The normal concentration of proteins in the blood plasma are as follows :

Normal plasma proteins

	Mean (g./100 ml.)	Range (g./100 ml.)
Total protein	6·8	5·8–7·8
Albumin	4·3	3·5–5·6
Globulin	2·2	1·6–3·1
Fibrinogen	0·3	0·2–0·4

All the known circulating protective antibodies are concentrated in the globulins of the plasma, as also are most of the protein fractions responsible for the carriage of lipids, sterols and iron. It is a remarkable fact that the human body maintains the level of its plasma globulins, even in the face of a severe lack of dietary protein. If parasitic or bacterial infections are present, the plasma level of the gamma globulins which include the protective antibodies may actually be increased above normal, despite protein deficiencies elsewhere in the body. The fraction of the plasma proteins affected by protein depletion is the albumin, which is often reduced in consequence. There is no known pathological condition in which the plasma albumin is elevated. Indeed it is a useful maxim of chemical pathology that *the plasma albumin may be normal or reduced : the plasma globulin may be normal or increased.*

It was popular in the past to describe the state of the plasma proteins in terms of the albumin/globulin (A/G) ratio, but this description is now passing out of fashion since it adds little to the understanding of the chemical pathology involved. Furthermore it confuses two essentially different pathological processes, *i.e.* one in which the globulins are raised in amount through infection or other causes and the other in which the albumin is reduced by protein depletion.

A fall in plasma albumin as a result of protein deficiency leads to diminished osmotic pressure of the blood. The great physiologist, Starling, first propounded the view that reduction of the osmotic pressure of the blood resulted in the passage of fluid from the vascular system into the tissues, with consequent œdema. It is now generally agreed that lack of protein, though frequently an important factor in ‘ famine œdema,’ is not the sole cause (Chapter 26); nevertheless, in cases of œdema suspected to be chiefly nutritional in origin, it is useful to determine the concentration of plasma albumin ; if it is reduced, the patient will benefit by an increase of protein in his diet.

Secondary or ‘ conditioned ’ protein deficiency may arise, despite an apparently adequate intake of protein, as a result of a variety of pathological processes, the chief of which are :

1. Loss of protein in the urine as a result of chronic disease of the kidneys.
2. Loss of protein (albumin and globulin) from the body by other routes such as hæmorrhage and serous exudates from wounds, or repeated removal of protein-containing fluid from the abdominal cavity.
3. Failure to absorb the proteins of the diet in various disorders of the intestines.
4. Failure by a damaged liver to carry out the synthesis of proteins (particularly albumin and fibrinogen) in adequate amounts from the amino acids absorbed from the intestines.
5. Damage to tissues (trauma). A great variety of traumatic injuries such as burns, fractured bones or surgical operations, are followed by a period of negative nitrogen balance. More tissue protein is catabolised than the diet can immediately replace. The breakdown is not confined to the immediate site of the trauma ; it seems to be part of a general reaction of the body to damage (Chapter 47).

THE NEED FOR DIETARY PROTEIN

Proteins in the diet supply the amino acids required for the *growth* of young animals, infants and children and also those needed for the *maintenance* of the tissues in adults. The amounts needed for growth are much greater than those for maintenance. The newborn human infant probably needs about five times as much protein as the adult per unit of weight. As the child develops the rate of growth slows down and so the need for protein is progressively reduced, but for a long time it remains much larger than the adult's. Protein deficiency is widespread in Africa, Asia and Latin America. It takes the form of the disease known as kwashiorkor, which is described in Chapter 28. Kwashiorkor is essentially a disease which affects the child who has been recently weaned. Needs for protein are still high and, if the child is deprived of the maternal supply of milk and given an inadequate protein diet, kwashiorkor develops. Direct evidence of protein deficiency in adults is much less frequently found. However, it is likely that there are large numbers of adults in under-developed countries whose health is impaired by lack of adequate dietary protein, although there may be no obvious clinical signs of deficiency.

Amino acids are not only necessary for growth and maintenance of tissues, but can also be used as a source of calories. If the caloric content of diet is inadequate, the protein in it will be used to supply energy. The dietary amino acids will be oxidised for this purpose and hence will not be available for building new tissues. In consequence protein deficiency is much more likely to occur if a diet is lacking in calories.

In all prosperous societies intakes of dietary protein by adults are usually well above the physiological minimum requirements. Psychological and social factors as well as physiological needs determine intake. These will be discussed first in relation to the adult ; the needs of children are considered on page 85.

Much study has been devoted to the solution of three problems :

1. What is the minimum amount of dietary protein on which normal human life and activity can be sustained ?
2. What is the desirable or optimal intake of protein for a man who has a free choice of food ?
3. Is a high-protein diet beneficial or harmful ?

In attempting to answer the first question it is necessary to remember that the diet must supply sufficient amounts of the essential amino acids, which the body cannot make for itself in adequate quantities from other amino acids. Furthermore, the diet must provide sufficient protein to maintain nitrogenous equilibrium.

There is much individual variation in the minimum amount of protein that must be fed in order to maintain nitrogenous equilibrium. Sherman (1920*a*) reviewing all the evidence from European and American sources, concluded that the range of variation lay between 21 and 65 g./70 kg. body weight/day, with an average of 44 g.

Probably most people could maintain nitrogenous equilibrium on about 45 g. of good-quality protein daily for long periods. Nevertheless a diet containing so little protein would be monotonous and unappetising to the great majority of Americans and Europeans, accustomed as they are to eating a varied diet providing up to 100 g. (or even more) of protein daily, much of which comes from animal sources.

The second and third questions are important, since they raise the practical issue as to whether our present dietary habits provide the right amount of protein for our needs and, were we to increase our protein intake considerably, how would it affect our health ?

$$\frac{25 \times 20}{500}$$

The American physiologist Chittenden (1909) attempted to answer these questions by keeping healthy adult males, including himself, on diets containing as little as 40 g. of protein daily for periods of up to one year. Chittenden asserted that this regime not only maintained, but often increased physical and mental vigour. He argued that reduction of the protein intake to the low levels used in his experiments is actually beneficial, claiming that the extra work in excreting the nitrogen from intakes of protein higher than this throws a strain on the kidneys and tends to cause renal and vascular disease.

However there is now good evidence that the human kidneys can excrete the nitrogenous end-products from large protein intakes without suffering damage provided that there is a sufficient excretion of water to carry it. For example, the Eskimo who traditionally lives on a diet largely composed of meat providing two or three times as much protein as the average European consumes, is apparently not more susceptible to renal and vascular disease on this account. The Australian range-rider, the gaucho of the South American plains and the Masai warrior of Central Africa all build up and maintain their good physique on diets which contain anything up to 250 or even 300 g. of protein daily. Provided the diet is otherwise properly balanced, a high protein intake seems to be tolerated throughout a lifetime without ill-effects. Nevertheless Chittenden's observation that adults can maintain good health on protein intakes far below current Western European and North American standards still remains true, and is a valuable contribution to knowledge.

In the opposite camp to Chittenden and his school are those who advocate a high protein diet, maintaining that protein restriction over long periods may be harmful. As early as 1881, Carl Voit, the great German pioneer in the scientific study of human nutrition, suggested 145 g. as a suitable daily allowance of protein. But the chief exponent of the view that a high protein intake, by promoting vigour and physical efficiency, is the *sine qua non* for ' superior ' men was the German physiologist, Rubner. In the Germany of 1914 he was a man of considerable influence, and probably did more than any army general to lose the war that then began; for on his advice German agriculture was continued on the old policy of rearing large herds of cattle and sheep. No additional pastures were ploughed. His failure to realise that cereals can yield up to six times more calories per acre than cattle contributed importantly to the defeats which followed in 1917. When food became short in Central Europe as a result of the Allied blockade, it was then too late to increase cereal production effectively. This mistake was avoided in Great Britain during the war of 1939-45 when the late Sir Jack Drummond was Scientific Adviser to the Ministry of Food.

A study of the dietaries of different races throughout the world shows that there is a great variation in the amount of protein on which man can subsist. The traditional diet of the Eskimos, as already mentioned, contains large amounts of protein which may supply as much as 40 per cent. of the total calories ingested. By contrast the protein in the diet of rice-eaters in most parts of South East Asia provides less than 10 per cent. of the total calories. Attempts to relate racial constitution to dietary habits have often tended to support the view that generous intakes of protein are desirable—as for example Sir Robert McCarrison's (1936) comparison between the poor physique of rice-eating Bengalis and the good physique of milk-drinking Sikhs. It is certainly true that in the age-old struggle of mankind against poverty and destitution, whenever it has been possible to raise the standard of living above the level of bare subsistence, there has been a rapid improvement in health which is usually associated with an increased consumption of protein. Throughout the world the most vigorous and energetic people eat considerably more protein than the minimum necessary to maintain nitrogenous equilibrium. But to equate their vigour with their protein intake is obviously an over-simplification of the issues involved. A better standard of living leads to improved health in a great variety of ways, of which a more varied diet is only one. Such a diet has not only a better protein content but also supplies increased amounts of minerals, vitamins and calories. The only justifiable conclusion is that active, energetic people generally contrive to obtain for themselves a pleasant and varied diet, the attractions of which are enhanced by foods of animal origin that incidentally contain ample amounts of protein.

DIETARY SOURCES OF PROTEIN

The protein content of almost every food used by man has been determined by the chemical method of estimating the total nitrogen and multiplying by 6·25 or other appropriate factor (p. 13). The protein content is expressed as g./100 g. of food in all well-known food tables. This does not relate the protein to the energy content of the food. Table 5, 1 gives the protein content of some common food expressed as g./100 Cal. and also the proportion of the calories in the food provided by protein. Most satisfactory human diets provide from 10 to 15 per cent. of the calories in the form of protein. The table enables one to distinguish at a glance foods which are poor, adequate and good as sources of protein in relation to their caloric content. The low protein content of cassava and bananas is important. In those countries where these foods are the main source of calories, protein deficiency is widespread.

The quantity of protein in a food, however, may be misleading as a measure of its value for growth or maintenance of tissue. The quality of the protein is also important and must now be discussed.

THE QUALITY OF PROTEINS

The nutritive value of a protein depends to an important degree on the relation of the amino acids in its molecule to those required for building

TABLE 5, 1. *Protein content of various foods, expressed as g./100 Cal. and as their contribution (per cent.) to the total calories provided by each food*

Value of foods as a source of protein	Protein content	Cal. provided by protein
Poor—	g./100 Cal.	per cent.
Cassava	0·83	3·3
Cooked bananas (plantains)	1·0	4·0
Sweet potatoes (*Ipomoea batatas*)	1·1	4·4
Rice (white, milled)	1·7	6·8
Taros	1·7	6·8
Potatoes	1·9	7·6
Millet (*Eleusine coracana*)	2·0	8·0
Rice (home-pounded)	2·0	8·0
Yams	2·3	9·2
Adequate—		
Maize (whole-meal)	2·6	10·4
Millet (*Setaria italica*)	2·9	11·6
Sorghum (*Sorghum vulgare*)	2·9	11·6
Wheat flour (medium extraction)	3·3	13·2
Millet (*Pennisetum glaucum*)	3·4	13·6
Good—		
Groundnuts (peanuts)	4·7	18·8
Cow's milk (3·5 per cent. fat)	5·4	21·6
Beans and peas	6·4	25·6
Beef (thin)	9·6	38·4
Cow's milk, skimmed	10·0	40·0
Soya bean	11·3	45·2
Fish, fatty	11·4	45·6
Fish, dried	15·3	61·6

Adapted from BROCK & AUTRET (1952).

new tissues. If the protein of the diet is seriously deficient in one or more of the essential amino acids, it is unlikely that nitrogenous equilibrium can be sustained, no matter how complete and excellent the diet may be in all other respects. If, however, another protein containing the missing amino acid in adequate amounts is added to the diet, nitrogenous equilibrium and normal nutrition can be established. This capacity of proteins to make good one another's deficiencies is known as their *supplementary value.* Thus gelatin will enhance the value of wheat-flour protein (Chick and Slack, 1945). Though gelatin is an imperfect protein, containing no cysteine or tryptophan, it nevertheless contains good amounts of glycine and hydroxyproline, two amino acids that are deficient in wheat. Similarly the protein of pulses, and especially soya flour, have considerable supplementary value when added to cereals (Chick and Slack, 1946) ; so much so that the mixture can go a long way towards providing a satisfactory substitute for milk in the diet of young children when supplies of milk are insufficient (Dean, 1953). The pulses, though poor in sulphur-containing amino acids, contain good amounts of lysine which is lacking in cereals. A protein such as egg albumin containing all the essential amino acids in good amounts is clearly nutritionally superior to the proteins of maize which contains little tryptophan or lysine. Thus proteins have different *biological values.*

Biological value

The biological value of a protein can be experimentally estimated in two ways: (1) The nitrogen balance method expresses the biological value as the percentage of the absorbed dietary nitrogen that is retained when the protein under investigation forms the only source of nitrogen in the diet. Biological values of proteins are conveniently determined on rats. However, man can also serve as the test animal. Results on the two species are essentially similar. (2) The growth method consists in determining the amount of the particular protein to be added to a protein-free diet in order to secure optimal growth, generally in young rats. By means of these methods proteins have been divided into two main groups, those of high and those of low biological value (Allison, 1955). As might be expected, the proteins of animal origin are generally of high biological value and hence have been called first-class proteins. In the animal group, egg and milk proteins have the highest biological value, next come the proteins of certain organs (liver and kidney and heart) and thirdly the proteins of meat and fish muscle and of the remaining organs. Not all animal proteins, however, are so good; gelatin for instance—a protein extracted from the collagen of connective tissue—is (as already mentioned) devoid of tryptophan and cysteine and deficient in other amino acids. It would therefore not support life as the only source of amino acids in the diet. In this sense its biological value is nil. Nevertheless, gelatin possesses undoubted nutritive value as a supplementary protein.

Net Protein Utilisation (*N.P.U.*) is an index which combines a measure of the biological value and also of the digestibility of the protein in a diet.

$$\text{N.P.U.} = \text{biological value} \times \text{digestibility}.$$

The N.P.U. is, perhaps, the best index of the quality of dietary protein.

Net Dietary-protein Value (*N.D-p. V.*) is an index which combines a measure of both the quality and quantity of dietary protein. The term has been introduced by Platt and Miller (1959), who define it as follows :—

$$\text{N.D-p.V.} = \text{N.P.U.} \times (\text{nitrogen in the mixture assayed} \times 6{\cdot}25).$$

This single index of the nutritive value of the protein in a diet will probably be increasingly used in the future.

Plant proteins are in general of lower biological value than animal proteins and so have been called second-class proteins. This is a purely relative term. As Table 5, 2 shows, some plant proteins are of good biological value and better in this respect than some animal proteins. It has long been known that plant proteins supplement each other and suitable mixtures have first-class nutritive qualities. This is of very great

TABLE 5, 2. *Biological value of proteins*

	Per cent. of absorbed nitrogen retained when foodstuff indicated is the sole source of nitrogen	References
Animal Origin—		
Whole egg	94	Mitchell and Hamilton (1929).
Milk	85	
Beef liver	77	
Pork ham	74	
Beef muscle	69	
Vegetable Origin—		
Various millets	80–90	Swaminathan (1937).
Rice	80	
Potatoes	78	Mitchell and Hamilton (1929).
Whole wheat	67 ; 66	Mitchell and Hamilton (1929) ; Swaminathan (1937).
Oats (rolled)	65	Mitchell and Hamilton (1929)
Maize	60	
Various pulses	40–60	Swaminathan (1937).
Mixed Diets—		
At various Air Force stations in Great Britain, 1943	79–82	Macrae *et al.* (1943).
Rice diets	66–81	Basu and Basak (1939).

practical importance since the supply of animal protein, notably milk for growing children, is and will be inadequate for human needs in many countries for several generations to come. Even with the best will in the world, dairy herds cannot be built up in a day.

AMINO ACID CONTENT OF FOODS

Biological methods had to be used to assess the quality of proteins when there was no adequate means for estimating their amino acid content. Chemical analyses of a few proteins have been available for a long time. However, it was not until the development in the last 15 years of chromatographic and microbiological methods that a systematic analysis of amino acids in all common food proteins became possible.

Table 5, 3, taken from an FAO (1957) report, gives the amino acid content of some common foods.

The data on which this table was based has subsequently been published in more detail in the U.S.A. by Orr and Watt (1957), with full references and much added information. This useful compilation of existing data shows the wide range of results obtained by different workers for the amino acid content of the same food. Another very full summary of the information available on the nutritive value of proteins, as determined by biological methods, and their chemical composition in terms of amino acid content, is available from India (Kuppuswamy *et al.*, 1958).

The data in Table 5, 3 are expressed in terms of mg. amino acid/g.

TABLE 5, 3. *Essential (and related) amino acids in the provisional pattern of amino acids and in selected foods (mg. amino acid/g. nitrogen) and protein scores*

Item	Isoleucine	Leucine	Lysine	Phenyl-alanine	Tyrosine	Sulphur-containing acids		Threonine	Tryptophan	Valine	Protein Score
						Total	Methionine				
Provisional amino acid pattern	270	306	270	180	180	270	144	180	90	270	100
Milk (cow's)	407	630	496	311	323	*211*	154	292	90	440	78
Egg	428	565	396	368	274	342	196	310	106	460	100
Casein	402	628	497	334	367	*215*	190	272	85	448	80
Egg albumin	403	556	372	392	271	397	245	275	90	486	100
Beef muscle	332	515	540	256	212	237	154	275	*75*	345	83
Beef heart	317	558	513	283	232	*217*	149	288	81	360	80
Beef liver	327	577	468	315	234	*226*	147	302	94	393	84
Beef kidney	304	542	453	294	232	*208*	128	278	92	365	77
Pork tenderloin	320	462	515	240	225	*233*	156	292	80	302	86
Fish	317	474	549	231	159	262	178	283	*62*	327	70
Oats	302	436	*212*	309	213	211	84	192	74	348	79
Rye	253	398	244	285	209	*217*	89	190	76	301	80
Rice	322	535	236	307	269	222	142	241	*65*	415	72
Corn meal (maize)	293	827	*179*	284	385	197	117	249	*38*	327	42
Millet	374	583	*190*	247	...	430	254	254	80	445	70
Kaoliang	351	834	*178*	420	128	205	93	223	70	381	66
White flour	262	442	*126*	322	174	192	78	174	69	262	47
Wheat germ	269	412	344	208	200	*165*	99	333	56	322	61
Wheat gluten	261	426	*107*	308	192	223	100	151	60	264	40
Groundnut flour	258	376	217	315	226	*150*	56	169	70	306	56
Soya flour	333	484	395	309	201	*197*	86	247	86	328	73
Sesame seed	300	500	*159*	460	244	317	181	182	93	216	59
Sunflower seed	296	402	*195*	275	149	197	95	209	78	313	72
Cottonseed meal	236	368	269	325	164	*188*	88	221	74	308	70
Potato	260	304	326	285	*99*	159	87	237	72	339	56
Navy bean	358	541	460	347	245	*126*	64	274	58	379	47
Peas	336	504	438	290	245	*157*	77	230	74	317	58
Sweet potato	283	345	293	355	281	*219*	119	324	115	484	81
Spinach	275	461	367	295	*127*	239	115	285	101	352	70
Cassava	118	184	310	133	98	*60*	22	136	131	144	22

Italicised items are those lowest in relation to the provisional pattern of amino acids and are the basis for the protein score.

nitrogen. This facilitates comparisons between the qualitative virtues of various foods as sources of a particular amino acid. It would be necessary to have a companion table giving the total nitrogen in each food in order to assess the quantity of a given amino acid that any one food might supply. The chief advantage of this table is that figures in italics indicate the qualitative weakness of a particular food in respect of an individual amino acid. A quick inspection in the same column will show a higher figure for some other food. This second food would compensate for the weakness of the first in this respect and thus would have supplementary value if taken in the same meal.

No one would pretend that Table 5, 3 is the last word on this subject. It is reproduced here because it has been widely studied and discussed, and because it represents a useful summary of present progress in this field.

PROTEIN SCORES

The reader will have noticed that the last column in Table 5, 3 is an item ' Protein Score.' This score is an attempt to mark the quality of a particular dietary protein, as judged by its amino acid content. Marks are out of 100, which is scored by a biologically ideal protein. Biological methods of assay are always time-consuming and expensive. If protein scores give the same assessment of the quality of a protein as the biological value, then they can be used as a practical and simple method for judging the quality of mixtures of protein in a diet.

Block and Mitchell (1946) were pioneers in attempts to give to individual proteins a score, and Oser has extended their observations during many years' work which he has recently reviewed (Oser, 1959). Both these workers have used egg albumin as a standard. It is as nearly completely utilised by the rat, the dog and man, as any food protein and is not significantly enhanced in biological value by supplementation with any amino acid. FAO have, however, used as a reference standard a provisional amino acid pattern (Table 5, 3, line 1). This is based on knowledge of requirements of healthy human beings for amino acids. Table 5, 3 shows that egg and egg albumin contain more of the essential amino acids than does the FAO reference standard.

In the FAO report the score for a protein is calculated in the following manner. The content of each amino acid in the protein is checked against the reference pattern. The amino acid which falls short of the reference is noted and called the limiting amino acid. For instance in Table 5, 3 the protein of beef muscle has a tryptophan content of only 75, as against 90 in the standard ; the content of all the other amino acids in beef protein exceeds that of the standard. Tryptophan is therefore the limiting amino acid for beef, which has a protein score of $\frac{75}{90} \times 100 = 83$. For white flour from wheat, lysine is the principal limiting amino acid with a value of 126 against the standard of 270 ; the protein score is $\frac{126}{270} \times 100 = 47$.

In general the protein score and the biological value of a food protein have usually been shown to be of the same order. However, there is still much to be learned about the range of variation of the amino acid content of foods and the range of variation of the amino acid requirements of man. Until additional data have been collected, it is impossible to assess precisely the quality of a protein as given by its protein score. In our opinion the protein score is likely to prove a useful rough index of quality if employed by those with a clear knowledge of its limitations. Statisticians and others who use protein scores for purposes of planning food policies, without due consideration of their biological limitations, may find that some of the results based on such conclusions are unsatisfactory.

THE AMINO ACID REQUIREMENTS OF MAN

Since pure amino acids became available on a large scale for experimental purposes, it has been possible to feed human beings on artificial diets in which a mixture of amino acids is the sole source of nitrogen. If then one of the essential amino acids is omitted from the mixture, an adult subject will cease to remain in nitrogen equilibrium and the growth of an infant or young child will be greatly impaired. The missing amino acid can then be replaced in gradually increasing amounts, until the subject is again in nitrogen balance or until normal growth is resumed. In this way an estimate of the human requirements for each of the amino acids can be made.

Table 5, 4. *The essential amino acid requirements of infants and adults (mg./kg./day).*

	Infants	Adult men	Adult women
Histidine	34	...	...
Isoleucine	126	10·4	5·2
Leucine	150	9·9	7·1
Lysine	103	8·8	3·3
Methionine (in presence of cystine)	45	...	3·9
Phenylalanine (in presence of tyrosine)	90	4·3	3·1
Threonine	87	6·5	3·5
Tryptophan	22	2·9	2·1
Valine	105	8·8	9·2

Such experiments are difficult and tedious and require much care and patience from both the investigators and their subjects. In the U.S.A. estimates of human requirements of amino acids have been made for adult men (Rose *et al.*, 1955), for adult women (Leverton *et al.*, 1956) and for infants (Holt *et al.*, 1960). So far as we are aware no studies have been made on growing children and adolescents. Table 5, 4 gives a summary of the findings. The first response to this table must be one of admiration for the investigators who have carried out these laborious studies. The second must be one of caution. Each figure is the mean of more than one observation, and values for individuals may vary greatly. The general agreement between the figures for men and women, obtained in different laboratories is good. With the exception of valine, the figures for men are higher. This may be because the requirements are expressed in terms of kg./body weight. Women on average are fatter than men and the agreement would probably be closer if results could be expressed per kg./lean body mass (p. 4).

The values for infants are very much higher than those for adults.

Infant requirements would however be fully met (but with little to spare) if the infant is given cow's milk providing 2 g. protein/kg./day. There can be little doubt that during the first five years of life children's needs for amino acids are very much greater than in adult life. Table 5, 5 (p. 87) gives FAO estimates of minimum protein requirements throughout childhood and adult life. The FAO Committee emphasise the tentative nature of the figure in this table.

All these estimates of amino acid requirements are only of value if the diet also supplies adequate amounts of calories and non-essential amino acids. If these are not available, the essential amino acids may be utilised in their place as sources of energy.

RECOMMENDED ALLOWANCES FOR PROTEIN

Obviously the requirement for protein of an individual depends on many variable factors, *e.g.* the daily turnover of protein within the body, its powers of converting one amino acid to another and its particular needs for certain enzymes and hormones. All these are the basic biological phenomena that distinguish one individual from another and make it impossible to predict with precision the amount of protein that a particular person is likely to need. The only practical policy is to frame recommended allowances in such terms that they are sufficiently liberal to provide for all but exceptional requirements.

The League of Nations Technical Commission on Nutrition (1936*a*) was the first authoritative body to attempt to answer the question: What is the desirable or optimal intake of protein for a man who has a free choice of food? They provided a definition of desirable consumption levels for protein. This Commission was influenced by the views of Sherman (p. 77). Allowing for a reasonable margin of safety, the Commission recommended that in practice the protein intake of adults should not fall below 1 g. of protein/kg. body weight/day. The protein should be derived from a variety of sources, partly of animal origin. This recommendation was subsequently adopted by the Food and Nutrition Board of the U.S.A. National Research Council (Chapter 15) and the 1953 revision of the recommended daily allowances.

The Committee on Nutrition of the British Medical Association considered that a better way of deciding the adequacy of a diet in respect of proteins is by reference to the contribution that the proteins make to the total calories. This Committee believed that " 14 per cent. of the calories in the form of protein of a mixed diet is sufficient for pregnant and nursing mothers, infants, children and adolescents. For adults (other than pregnant and nursing women), the Committee recommends that the diet should provide not less protein than an amount representing 11 per cent. of the energy allowance." These recommendations were based on the evidence that growth and health were well maintained in Great Britain between 1940 and 1945 when the energy derived from protein generally represented 10 to 14 per cent. of the total calories provided for the population. This method has obvious advantages when planning food supplies for people living on very poor diets. These advantages are clearly demonstrated by the data in Table 5, 1, which shows the foods which are likely to result in protein deficiency if too much reliance is placed on them. It should be noted, however, that in the practice of dietetics in Great Britain and other Western countries, it matters little whether the N.R.C. or B.M.A. standards are used.

In making use of the B.M.A. standards of recommended allowances, as given in Chapter 15, it is necessary to realise that those for protein are derived directly from the caloric allowances and have no independent origin. Thus, although the allowances of protein appear to increase with the amount of physical work that needs to be done, this is not intended to mean that this is necessary or desirable. It should be recognised as inevitable that as the amount of food eaten increases to provide for additional caloric needs, the amount of protein must be greater if the diet is to continue to be normal in composition. Thus workers in heavy industries are likely to ingest 100 to 150 g. of protein daily. Yet there is no evidence that they really need so much ; indeed there is no evidence that physical activity has any effect on the amount of protein utilised by the body.

Table 5, 5. *Average minimum requirement of reference protein and safe practical allowances (g./kg. body weight).*

Age	Minimum requirement	Safe practical allowance *
Newborn . . .	2·0	...
9 months . . .	1·4	2·73
2 years . . .	1·1	2·15
5 years . . .	0·8	1·56
9 years . . .	0·7	1·37
Adolescent . . .	0·8	1·56
Adult	0·35	0·68

* Assuming a protein score of 76.

The method recommended by the FAO Committee (1957*b*) to calculate protein requirements takes into account both the quantity and quality of the dietary protein and the age, sex and weight of the consumer. The recommended minimal requirements of reference protein, which provides all the essential amino acids in accordance with the provisional pattern related to age are shown in Table 5, 5. Additional allowances are made to cover the special requirements during pregnancy and lactation. If the protein score of the diet is less than 100 (Table 5, 3) the minimum requirement for protein of such quality is correspondingly greater. For example, an adult man requires 0·35 g./kg. of reference protein which scores 100, but his minimum requirement for protein which scored only

50 would be 0·7 g./kg. body weight. The Committee suggested an arbitrary increment of 50 per cent. over the average minimum requirements to cover individual variability, and this higher figure was called the safe practical allowance. In the example just given with a protein score of 50 the safe practical allowance would be 0·9 g./kg. body weight.

Comment.—Only in the last 20 years has it been realised that the most important deficiency disease in the world is kwashiorkor, which is due to lack of proteins ; in the same period new knowledge has been obtained about human requirements of amino acids and their distribution in different food proteins. There is a natural desire that this new medical and physiological knowledge should be summarised and simplified into a form which could be understood and used as a practical guide by agricultural planners. Protein deficiency can only be prevented by carrying out a sound agricultural policy in the countries in which it is common.

The FAO Report on Protein Requirements is an attempt at such a summary. A real difficulty in the implementation of the report arises out of the fact that the protein requirements of young children are relatively so much greater than those of adults. There are many areas in the world where the protein supply would appear to be adequate, judged by the FAO standard, and yet where kwashiorkor is common. The explanation of this apparent anomaly is that protein is usually not distributed amongst the members of a family according to their physiological needs. In almost all countries custom determines that the adult male members of the family, the breadwinners, get the major portion of meat and other protein-rich foods in the family diet. Only after they have received what they wish is the remainder divided amongst the women and children. Custom, sometimes supported by taboo, works against a distribution according to physiological needs. For this reason the use of the figures provided in Table 5, 5 or in any future table drawn up by an international committee of repute will only be a reliable guide to the protein requirements of a region or a country if both dietary customs and physiological needs are taken into consideration.

CHAPTER 6

FATS

UNTIL recent years the fats in food have been regarded chiefly as a convenient and concentrated source of calories. Physiologists in the past have paid scant attention to the quality of the different dietary fats. A new interest in the chemistry and physiology of fats has lately arisen because several chronic degenerative diseases—of which the most important is atherosclerosis—have been attributed, at least in part, either to the quality or the quantity of the fats in food.

Unfortunately there is some confusion in terms. The housewife, when she goes to buy butter, margarine or lard, has a clear idea of what she means by fat. Biochemists, in an effort to be more precise, have invented a new word—lipid—which covers all the chemical substances included in the housewife's fat—triglycerides, phospholipids, sterols, etc. Lipids have been defined as substances which are: (1) insoluble in water but soluble in organic solvents such as ether, chloroform and benzene; (2) actual or potential esters of fatty acids; (3) utilisable by living organisms. But these criteria cannot be applied too rigidly or exclusively. The chemist uses the term ' fat ' in a restricted sense to mean the ' neutral fats ' which are mixtures of esters of fatty acids. Finally there is the term ' oil ' which is unfortunately applied both to liquid digestible triglycerides (such as olive oil) and to indigestible mineral hydrocarbons (such as liquid paraffin).

Hereafter we shall use the word ' fat ' in the housewife's sense when referring to the fat content of foods and diets, but shall follow the more precise chemical nomenclature when considering the metabolism of lipids in the body.

In practical dietetics it is useful to refer to *table fat*, meaning butter and margarine. This is convenient as table fat can be accurately measured and therefore accurately prescribed. In contrast, the total fat in a diet is hard to measure, because different samples of the same food may vary widely in fat content, especially in the case of meat. Accurate assessments of the total fat in a diet are thus very difficult to obtain without a chemical analysis of samples of the diet as actually consumed.

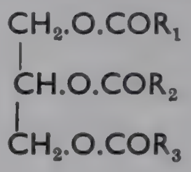
The fats in the body are sometimes considered under two separate heads: *l'élément variable* and *l'élément constant*, as first proposed by Terroine, the distinguished French physiologist. The first is the fuel store of the body which can be expended; the second is part of the essential structure of the cells. The chemistry and the physiology of these two components is very different, as explained later in this chapter.

CHEMICAL CONSTITUTION AND NATURAL DISTRIBUTION

The description of the lipids given below, as in many textbooks of physiology and biochemistry, is insufficient for a full appreciation of some of the modern aspects of their relation to disease. For a full account of the subject two large monographs (Hilditch, 1956 ; Deuel, 1957) and a smaller one (Lovern, 1957) are recommended for reference.

Triglycerides

This is the form in which fats chiefly occur both in foodstuffs and in the fat depots of most animals. Triglycerides are esters of glycerol and fatty acids and have the general composition :



$$\begin{array}{l} CH_2.O.COR_1 \\ | \\ CH.O.COR_2 \\ | \\ CH_2.O.COR_3 \end{array}$$

where R_1COOH, R_2COOH and R_3COOH are long-chain fatty acids with even numbers of carbon atoms. There are over forty different fatty acids found in nature. These give a diversity and chemical specificity to the natural fats similar to that given to the proteins by the twenty-three known natural amino acids. Characteristically fats are *mixtures* of triglycerides ; no fat found in nature consists of a *single* triglyceride.

A point of interest is that fatty acid molecules appear to be distributed amongst the glycerol molecules in any one fat according to the '*principle of even distribution*' (Hilditch). Thus in a mixture of triglycerides, molecules of a single fatty acid (say palmitic acid) will be attached first to every molecule of glycerol. Triglycerides containing 2 molecules of palmitic acid will not be found unless palmitic acid comprises more than a third of the total fatty acids present. Any fatty acid forming appreciably less than one-third of the total fatty acids will never occur more than once in any one triglyceride. Thus the composition of individual triglycerides is determined by *biological order* and is not the result of chemical chance.

Fatty acids occurring in nature can be classified into three types. First, there are the saturated fatty acids ; secondly, there are unsaturated fatty acids with one double bond (the monoethenoid acids) ; thirdly, there are unsaturated fatty acids with two or more double bonds (the diethenoid and polyethenoid acids). The degree of unsaturation in any fat plays an important part in determining its physical nature. Fats consisting predominantly of saturated fatty acids are solid at room temperatures, while those with a high proportion of unsaturated acids are usually liquid (*e.g.* whale oil, cod-liver oil and olive oil). The extent to which a fat contains unsaturated fatty acids can be assessed from its ability to take up iodine (the ' iodine number '). Vegetable and marine oils can be hardened and turned into solid fats by the action of hydrogen in the presence of a catalyst. This has enabled vegetable oils from all over the world to be used in the various processes of making margarine and other artificial butters such as *vanaspathis* in India. This hydrogenation converts most of the unsaturated fatty acids into saturated fatty acids.

Saturated fatty acids

These have the general formula $CH_3(CH_2)_nCOOH$, where n can be any even number from 2 to 24. The common ones are :

Lauric acid :	$CH_3.(CH_2)_{10}.COOH$
Myristic acid :	$CH_3.(CH_2)_{12}.COOH$
Palmitic acid :	$CH_3.(CH_2)_{14}.COOH$
Stearic acid :	$CH_3.(CH_2)_{16}.COOH$

Palmitic acid is widely distributed in nature and may contribute from 10 to 50 per cent. of total fatty acids in any fat. Of the other saturated fatty acids only myristic and stearic acid (the latter is present in up to 25 per cent. of beef fat) are comparable in distribution to palmitic acid, though they are not invariably present in every fat.

Unsaturated fatty acids with one double bond

The most important is oleic acid, which has the constitution :

$$CH_3.(CH_2)_7.CH{:}CH.(CH_2)_7COOH$$

Oleic acid is the most widely distributed fatty acid in nature. In most fats it forms 30 per cent. or more of the total fatty acids.

Unsaturated fatty acids with two or more double bonds

There are many of these acids (polyethenoid acids), but three are of special interest :

Linoleic acid :

$$CH_3.(CH_2)_4.CH{:}CH.CH_2.CH{:}CH.(CH_2)_7.COOH$$

Linolenic acid :

$$CH_3.CH_2.CH{:}CH.CH_2.CH{:}CH.CH_2.CH{:}CH(CH_2)_7.COOH$$

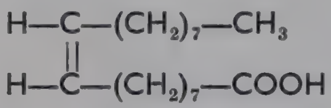
Arachidonic acid :

$$CH_3.(CH_2)_4.CH{:}CH.CH_2.CH{:}CH.CH_2.CH{:}CH.CH_2.CH{:}CH.(CH_2)_3COOH$$

These three acids are often referred to as ' essential fatty acids,' and sometimes abbreviated to EFA. As long ago as 1929, Burr and Burr showed that these acids were essential for the growth and well-being of rats. It is now known that they lower the levels of lipids in the blood of man and relative deficiencies of them may be responsible for degenerative diseases in both man and animals. The evidence for this will be discussed later in this chapter.

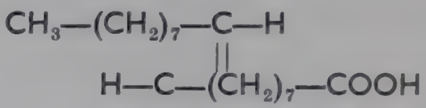
Cis and Trans Isomerism

Any fatty acid which contains a double carbon bond (ethylene linkage) can exist in either of two geometrically isomeric forms. This is known as *cis* and *trans* isomerism. When two carbon atoms are held together by the double bond, there is no freedom of rotation for these groups about the axis of the bond. Thus oleic acid, a cis form, has a trans isomer elaidic acid.



$$\begin{array}{l} H-C-(CH_2)_7-CH_3 \\ \quad\;\; \| \\ H-C-(CH_2)_7-COOH \end{array}$$

oleic acid (*cis*)



$$\begin{array}{r} CH_3-(CH_2)_7-C-H \quad\quad\quad\quad \\ \| \quad\quad\quad\quad\quad\;\; \\ H-C-(CH_2)_7-COOH \end{array}$$

elaidic acid (*trans*)

Most natural fatty acids exist in the *cis* form, though some *trans* forms are present in the natural fats of ruminants. *Trans* isomers of unsaturated acids are reputed to lack the ability possessed by *cis* isomers of lowering the level of lipoproteins in plasma (p. 103).

Distribution of Fatty Acids in Animal and Plant Life

The chemical constitution of the natural fats is related to the biological species from which they are derived. Organisms which have been classed together by biologists on morphological grounds have been found by chemists to share in general the same fatty acids in approximately similar proportions. Hilditch has been a pioneer in finding out the biological distribution of the fatty acids.

In fats from all *fresh-water life*, whether plant or animal, the predominant fatty acids are unsaturated and include those containing 16, 18, 20 and 22 carbon atoms in the molecule, in varying proportions and in different states of unsaturation. The only important saturated acid is palmitic acid, which is usually present as 10 to 18 per cent. of the total acids.

In the *marine world* unsaturated fatty acids with 20 and 22 carbon atoms in the molecule are most numerous. In highly developed fish and aquatic mammals, the fatty acids form esters with other higher alcohols as well as with glycerol. The fats present in salmon and sea-trout, fish which live both in fresh and salt water, have fatty acids which conform to the general picture of other marine animals.

In *land animals* and in particular mammals, the unsaturated oleic acid and the saturated palmitic acid predominate. Palmitic acid forms about 25 to 30 per cent. of the fatty acids in the depot fat of all the common mammals and this accounts for their hardness and low iodine value relative to marine oils. Stearic acid is found principally in the fat of ruminants, where it in part replaces oleic acid.

Milk fats, such as butter, differ from other animal fats by containing definite though small amounts of short-chain fatty acids with only 4 to 12 carbon atoms.

In *plant seeds* the fatty acids are less varied than in aquatic life. As in land animals, oleic acid and palmitic acid are prominent, but a third acid, linoleic acid, is also a frequent component. Linoleic and linolenic acids are amongst the most familiar constituents of the numerous seed oils. Coconut oil is an exception in that it is mostly made up of saturated fatty acids, with very little oleic and linoleic acid. Olive oil is very rich in oleic acid but contains little linoleic acid. The elucidation of the relationship of the different fatty acid components of the fats with the morphology and natural history of plants and animals from which they come is a fascinating biological problem.

A diet rich in linoleic and linolenic acid can be obtained by eating plenty of vegetable seed oils. Arachidonic acid seldom occurs in vegetable oils, but animals apparently have no difficulty in synthesising it directly from linoleic and linolenic acids.

The proportion of essential fatty acids that remains in vegetable and marine oils after hardening by commercial hydrogenation is naturally of great interest. Completely hydrogenated fats of course contain none. Until recently most margarines contained little or no EFA. With the steady increase in the consumption of margarine during the last 50 years in many countries, national intakes of EFA have probably declined. Recently, owing to the great interest in the possible physiological action of these acids, manufacturers have been at great pains to produce margarines containing EFA. Products are now advertised in which it is claimed that 28 per cent. of the fatty acids are polyunsaturated. This is achieved by skilful blending with vegetable oils, which have not been hydrogenated.

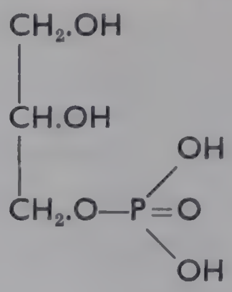
Waxes

As defined chemically, waxes are fatty acid esters of higher alcohols. They occur widely in the cuticle of leaves and fruit and in the secretions of insects. They replace the triglycerides to some extent in the tissues of aquatic animals (*e.g.* crustaceans). In some whales, wax esters form the major component of the depot fat. So far waxes have not been shown to be an important constituent of any of the higher land animals ; nor do they contribute importantly to normal human diets.

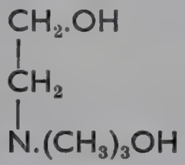
Phospholipids

After the triglycerides, the next largest lipid component of the body are the phospholipids. A great variety of these substances are present in the body.

Phosphatidyl esters are a most important class of phospholipids ; they are found predominantly in the tissues and blood, and to a much lesser extent in the depot fat. They are concerned in the mechanism of blood coagulation and also in the transport of fat about the body, as will be discussed later. Phosphoglycerol has the formula :

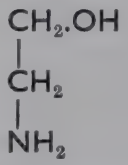


Phosphatidyl esters are derived from phosphoglycerol by esterification of the two —OH groups (the alcoholic radicles) with fatty acids and the attachment of a nitrogen-containing alcohol to the phosphate radicle. Three phosphatidyl esters are well known, each containing one of the following three bases or nitrogen-containing alcohols :



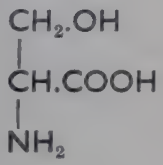
$$\begin{array}{l} CH_2.OH \\ | \\ CH_2 \\ | \\ N.(CH_3)_3OH \end{array}$$

Choline



$$\begin{array}{l} CH_2.OH \\ | \\ CH_2 \\ | \\ NH_2 \end{array}$$

Ethanolamine



$$\begin{array}{l} CH_2.OH \\ | \\ CH.COOH \\ | \\ NH_2 \end{array}$$

Serine

Phosphatidyl choline is the predominant substance of *lecithin*, as prepared from egg yolk. It was isolated from eggs over 100 years ago. It is now known that lecithin prepared by ordinary laboratory methods contains significant amounts of phosphatidyl ethanolamine and possibly other physiologically active substances. Nevertheless the absolute amount of these substances is small ; the term lecithin is nowadays employed as a synonym for phosphatidyl choline.

The constituent fatty acids in the phosphatidyls vary widely. Like the triglycerides, lecithin and related substances are not individual compounds, but each is a mixture. The distribution of the fatty acids does not appear to follow the even pattern characteristic of the triglycerides. Nor is there evidence of so close an association between the chemical constitution of the phosphatidyl esters and the biological species of their origin as in the case of the triglycerides. Most animal phospholipids are characterised by a large proportion of highly unsaturated fatty acids including arachidonic acid.

It is important to know something of the chemical nature of these phosphatidyl esters, because, as will be discussed later, active research is being carried out on their possible metabolic activities in relation to diet and the production of disease. There are a number of other related substances present in animal tissues about which little is yet known, but it would be unwise to assume that they have no nutritional importance. Some of these may be listed briefly.

Inositol phosphatides have not yet been adequately characterised chemically. They are, however, widely distributed in animal and plant tissues, together with phytic acid in the latter. It is possible that they are closely analogous to the phosphatidyl esters, with inositol replacing the basic alcohol in the molecule.

Cardiolipin is the factor in extracts of beef-heart responsible for the reaction with syphilitic sera, as used in the Wassermann test. It probably consists of a chain of 3 phosphoglycerol molecules and a diglyceride. Its normal role in the metabolism of heart muscle is quite unknown.

Lysophosphatides.—These are substances produced from lecithin by the action of an enzyme *lecithinase A* which is present in venom of cobras and certain other snakes. The enzyme splits off one of the two fatty acids in the lecithin molecule, but only one. The resulting lysophosphatide has a powerful destructive action on red blood corpuscles. Lecithinase A is now known to be widely distributed in plants and animals. Whether or not it plays a significant role in the physiological destruction of worn-out red cells is uncertain. Apparently the cobra has picked out some widespread enzymatic mechanism (of obscure function) and has been able to develop it enormously for its own specific purpose.

The **sphingolipids** are a class of lipids in which the glycerol is replaced by the substance *sphingosine*, which is both an alcohol and a base.

$$CH_3.(CH_2)_{12}.CH{=}CH.CH.(OH).CHNH_2.CH_2OH$$

Sphingomyelin is an important constituent of the myelin sheath of nerves. It contains the base sphingosine in place of glycerol, linked through a phosphate molecule to choline. A fatty acid (which is often lignoceric acid) is joined to the amino radicle. It thus has some structural resemblance to lecithin. In the *cerebrosides* sphingosine is linked with a hexose (usually galactose, but sometimes glucose) and a fatty acid is joined as in sphingomyelin to the amino radicle of the base. The molecule contains no phosphorus. The cerebrosides are widely distributed throughout the animal and plant kingdoms, but are found chiefly in nervous tissue.

Although the sphingolipids are an important chemical component of the nervous system, little is known about their metabolic behaviour or their origin in the body.

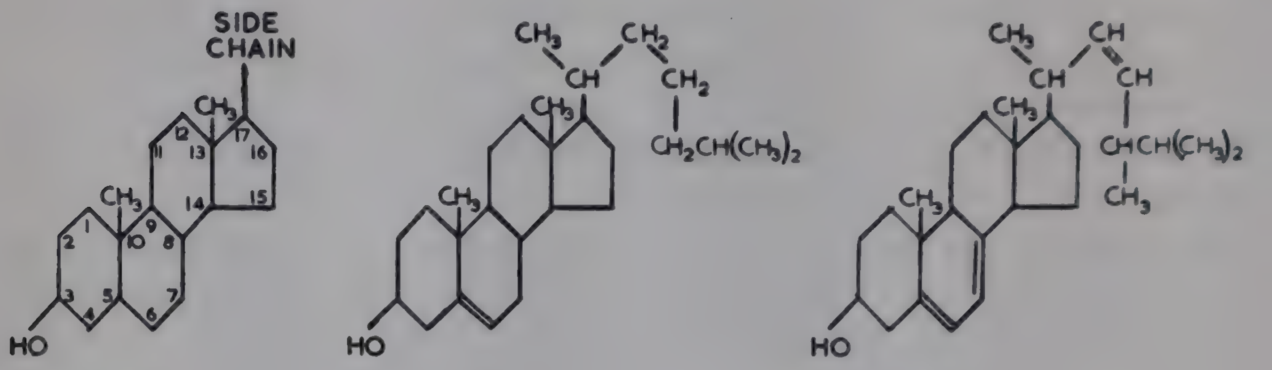
The Sterols

These comprise a most important class of biological substances, all of which have the same basic ring structure shown in Fig. 6, 1, A. Sterols are solid alcohols and, like all alcohols, can form esters with fatty acids and other organic acids.

Cholesterol (Fig. 6, 1, B) is the predominant sterol in the higher mammals. It is present in the blood, where it plays an important role in the transport of fatty acids. It is also present in all animal tissues, so that some cholesterol is present in all foods of animal origin, but eggs are the only common food rich in cholesterol. It is absent from foods of plant origin. However, it is not an essential nutrient since all mammals are capable of synthesising it.

The bile salts (sodium glycocholate and sodium taurocholate) are formed by the combination of the amino acids glycine and taurine with

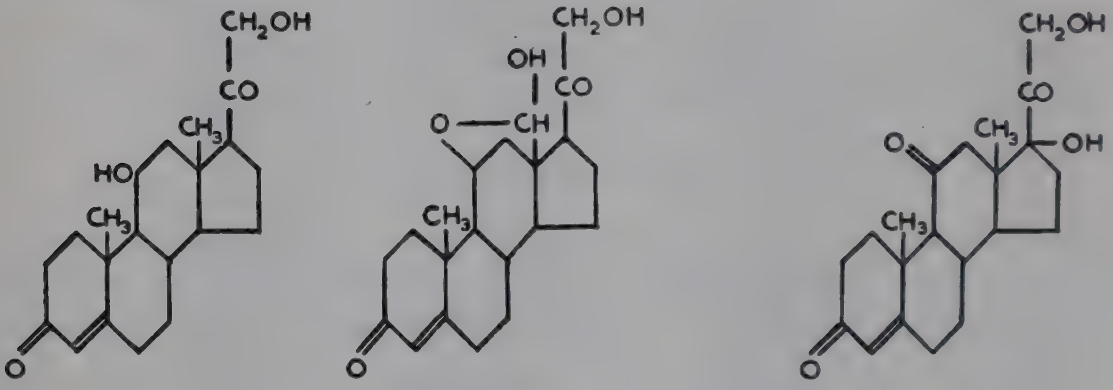
CHEMICAL CONSTITUTION OF STEROLS



A. general formula of sterols

B. cholesterol

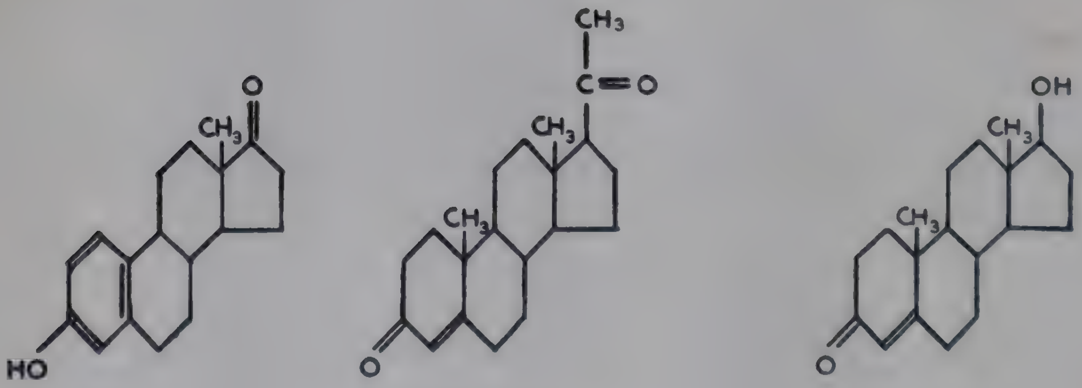
C. ergosterol



D. corticosterone

E. aldosterone

F. cortisone



G. oestrone

H. progesterone

I. testosterone

Fig. 6, 1

cholic acid which is a derivative of cholesterol. They are probably formed throughout the body, but are concentrated by the liver and excreted through the bile duct into the duodenum. There they play an essential role in the digestion of fat.

Ergosterol (Fig. 6, 1, c) is one of a group of sterols found in many plants, notably in yeasts and fungi. Under the influence of ultraviolet light it is converted into vitamin D, as also is 7-dehydrocholesterol which is the natural precursor of vitamin D in animal tissues (p. 201).

The adrenocortical hormones

Corticosterone (Fig. 6, 1, D) is one of the principal hormones of the adrenal cortex. It has many physiological actions of which perhaps the most important is the mobilisation of tissue proteins and the conversion of protein into carbohydrate.

Aldosterone (Fig. 6, 1, E) has an important role in the regulation of the electrolyte balance in the body.

Cortisone (Fig. 6, 1, F) is a synthetic substance with actions very similar to the naturally occurring cortical hormones. It or one of its analogues, such as prednisolone, is widely used in medicine, principally for the purpose of inhibiting allergic and inflammatory processes, which are either excessive in degree or which fail to respond otherwise. It has actions similar to corticosterone and aldosterone. Overdosage with cortisone may lead to hyperglycæmia and also to electrolyte imbalances.

The sex hormones.—The principal hormones produced by the ovary and testis are sterols (Fig. 6, 1, G, H, I). In addition to their specific actions controlling sexual function, they also have important metabolic effects. Thus progesterone can cause water retention and testosterone nitrogen retention. They determine the metabolic changes at puberty, at the menopause and during pregnancy.

The sex hormones undoubtedly affect in some way the metabolism and growth of many tumours. Sex hormone therapy has proved useful in the treatment of osteoporosis (Chapter 30) and also as a palliative in several types of cancer, but how these therapeutic effects are produced is, as yet, little understood.

DIGESTION AND ABSORPTION OF FAT

The role of the stomach.—Digestion of fat does not take place in the stomach since conditions there are unsuitable for emulsification which must precede digestion. The presence of fat in the food delays the emptying of the stomach. This may contribute to the feeling of satiety after a meal rich in fat. The mechanism of the delay has been attributed to the inhibitory action on the movements of the stomach of a hormone (enterogastrone), liberated when fat enters the duodenum.

Emulsification.—In the duodenum, below the point where the pancreatic juice and bile enter, conditions first become suitable for the emulsification of fats which must be reduced to particles of diameter 0·5 to 1 μ or less, before digestion and absorption are possible. Frazer *et al.* (1944) have shown that bile salts, small quantities of fatty acids, and monoglycerides liberated by pancreatic digestion, are able to cause emulsification either in a slightly acid or alkaline medium (*p*H range of 6·0 to 8·5), with the formation of droplets smaller than 0·5 μ, which remain stable for 3 hours. None of the three substances alone is an effective emulsifier under the conditions found in the intestine and there is every reason to think that this combination is the natural and necessary physiological mechanism concerned with the digestion of fat.

Hydrolysis of fats by lipases.—Both the pancreatic juice and the intestinal juice contain lipases, enzymes which split triglycerides into fatty acids, diglycerides and monoglycerides and also glycerol. Probably very little glycerol is formed and hydrolysis usually stops at the monoglyceride stage. The presence of bile salts renders the fatty acids more soluble in water. The contents of the small intestine are not sufficiently alkaline to allow the fatty acids liberated by hydrolysis to form soaps with alkalis under normal conditions.

Absorption

Lipids pass into the intestinal lymph and blood mostly as triglycerides. Resynthesis takes place partly in the intestinal lumen, where the pancreatic lipase has synthetic in addition to hydrolytic actions, and partly in the intestinal wall. The intestinal wall is rich in phospholipids, the fatty acids of which may be turned over rapidly. Probably a proportion of the free fatty acids liberated in the lumen pass through a phospholipid stage before being resynthesised into triglycerides. In the processes of digestion and absorption the fatty acids are mixed, so that the triglycerides of the food lose their identity and new triglycerides partly characteristic of the animal species are formed. After resynthesis the triglycerides enter the lacteals of the small intestine as small particles about 0·5 μ in diameter, known as chylomicra. The chylomicra pass up the mesenteric lymph vessels, enter the thoracic duct and thence join the systemic circulation via the right subclavian vein. In experimental animals it is not difficult to make a fistula in the thoracic duct and collect the chyle therefrom. In clinical medicine an occasional opportunity to study the formation of chyle arises ; if, as a result of injury, a leak occurs in the thoracic duct in the course of its passage through the thorax, the chyle escapes into the pleural cavity (chylothorax) and can be aspirated through the chest wall.

The major part of the fat absorbed enters the circulation via the thoracic duct. A small part, including most free short-chain fatty acids, may reach the liver via the portal blood.

The above description is the orthodox view of fat digestion and absorption. It was fully set out by Verzar and McDougall (1936) in a well-known monograph. It has recently been supported by a series of experiments which have been summarised and reviewed by Bergström and Borgström (1955). It should be emphasised that the digestion and absorption of fat is a very complex chemical procedure. It is usually easy to demonstrate the presence of a single chemical reaction, but very difficult to assess how important it is in the overall process. There may be important differences between various species, and relatively little work has been possible on man. Readers who wish to appreciate this very difficult subject should consult the review to which reference has already been made.

Fat absorption without hydrolysis (particulate absorption).—The very fine globules of fat in the chyle were first seen in the seventeenth century, soon after the discovery of the microscope. It has frequently been assumed that the emulsified fat in the intestines was absorbed direct, passing unchanged through the intestinal mucosa. That this can happen is proved by the observation that liquid paraffin is absorbed if given by mouth in a suitably fine emulsion. Liquid paraffin, of course, undergoes no hydrolysis ; it is only absorbed when given finely emulsified.

Whether food fat is absorbed to an appreciable extent without hydrolysis is a classic physiological dispute. Over 70 years ago the great German physiologist Pflüger, who was an upholder of the orthodox view that fatty acids and glycerol were absorbed separately after hydrolysis by lipases, was involved in controversy with Munk, who was the chief exponent of the view that fats were absorbed as finely divided triglycerides. In recent years the orthodox view has again been challenged, this time by Frazer (1946 and 1958) of Birmingham. Frazer's chief argument is that lipases would not be able to hydrolyse more than a small fraction of ingested triglycerides in the time that the food remains in the small intestine. However, he has so far failed to demonstrate, by direct histology, the droplets passing through the mucosal epithelium of the small intestine.

The controversy is by no means ended, but most physiologists consider that the greater proportion of the triglycerides are hydrolysed before absorption, though admitting the possibility that some unhydrolysed fat may on occasions pass through the intestinal mucosa.

Completeness of digestion and absorption of fat.—Most fats, when fed to adult subjects in quantities up to 100 g./day, are digested and absorbed to the extent of at least 95 per cent. Much larger quantities, up to 250 g./day or even more, can sometimes be absorbed if the body is short of calories. Arctic explorers and lumberjacks frequently consume and digest such large amounts (Butson, 1950). In constitutionally thin people there is no evidence of a failure to digest or absorb fats. Normally, fats never form more than 10 per cent. of the dry weight of the stools and the amount present is largely independent of the dietary intake. With a fat intake of 100 g./day or less, the presence of more than 7 g. of fat daily in the fæces (taken as an average over a period of at least 5 days) constitutes evidence of some failure of fat absorption and justifies a diagnosis of steatorrhœa. Steatorrhœa is found whenever there is a failure of secretion either of the bile salts or the pancreatic juice. It also occurs in the malabsorption syndrome (Chapter 38).

LIPIDS IN THE BLOOD

After absorption from the alimentary canal nutrients must be carried in the blood either to storage depots or to the muscles and other tissues, where they serve as a source of energy. They must also be taken from the storage depots to the active tissues when alimentary absorption is not taking place. In addition, nutrients must pass to and from the liver and other tissues, where synthetic processes and chemical transformation take place. For the transport of carbohydrate glucose serves as a convenient currency, for it is a simple chemical and readily soluble in water and almost all the carriage of carbohydrate throughout the body takes place in this form. Lipids are insoluble in water and for them no simple form of currency exists. They are carried in the blood in a variety of ways, but always attached in some manner to protein. Many different types of lipoprotein are present in blood. The elucidation of their complex nature is a difficult problem in physical chemistry ; much is still unknown about the physiological circumstances under which they are formed and broken down. There are three main types of lipoproteins in the blood, which are very different both in chemical structure and in physiological function. They may be considered separately. An excellent review of this difficult subject with 375 references is given by Olson and Vester (1960).

Chylomicra

These are particles about 0·3 to 1·5 μ in diameter which can be seen and counted under the dark ground microscope. Chylomicra are beyond question the chief vehicle for the carriage of lipids from the alimentary canal to the liver and fat depots. Chemically they are chiefly triglycerides and contain only about 1 per cent. protein. A small amount of phospholipid is present, which probably provides a covering layer giving stability to the particles (Robinson, 1955). They also contain a little cholesterol, both free and esterified.

ALIMENTARY LIPÆMIA.—After a meal containing fat, there is an increase in the number of chylomicra in the blood. These are removed by a clearing system, discussed on the next page. This mechanism clears the blood of lipid rapidly and, if only small amounts of fat (30 g. or less) are taken at a meal, it is difficult to detect any increase in the plasma lipids. The clearing of chylomicra from the plasma keeps pace with their formation in the intestinal wall. If a meal containing a large amount of fat is eaten, there is an increase in blood lipids, which can be easily demonstrated. The plasma becomes milky. Alimentary lipæmia can be followed quantitatively by counting the chylomicra, but this is a difficult technique and seldom employed. It is more usual to determine the rise in either total serum lipids or in serum triglycerides. Man and Gildea (1932) found that 3 hours after a meal containing 59 g. of fat, the total fatty acids in the sera of 9 subjects increased by 10 to 223 mg./100 ml. (mean 123). With a higher fat intake larger rises may be found. The rise is usually at a maximum 2 to 4 hours after taking the fat ; levels return to normal within 6 to 8 hours. As chylomicra contain only small amounts of phospholipid and cholesterol, the plasma level of these lipids is raised only very slightly by a fatty meal.

The clearing system.—Chylomicra are removed from the blood in a matter of minutes (Bragdon, 1959). This is effected by an enzyme system which hydrolyses the triglycerides and liberates free fatty acids (non-esterified fatty acids or NEFA). They can then be taken out of the blood and into the tissue cells, a process in which they are carried by serum albumin. The enzymes which clear the chylomicra from the blood are liberated after a fatty meal, from the tissues of several organs. Further details of this very complicated system are given in reviews by Robinson and French (1957) and by Korn (1958).

Of special interest is an apparent association between this chylomicron clearing system and factors controlling blood coagulation. The natural anticoagulant, heparin, affects both systems and may have a specific role in each. Phospholipids also affect blood coagulation under some circumstances. This has naturally led to speculation about possible associations between pathological blood coagulation *in vivo* and the transport of lipids in the blood. The basic observations are :—

1. Heparin when injected into an animal after a fatty meal causes a rapid clearing of the cloudiness in the plasma, which occurs during alimentary lipæmia (Hahn, 1943). Heparin, it will be remembered, is a natural anticoagulant which can be isolated from liver.

2. After a fatty meal, when alimentary lipæmia is at its height, the blood clots more readily (Fullerton, 1955).

3. It has long been known that crude lecithin prepared from egg yolk accelerates the clotting of blood in test tubes. This is not due to pure lecithin (phosphatidyl choline), but to the related phosphatidyl ethanolamine, which forms about 7 per cent. of the total phosphatide in most preparations of lecithin. Phosphatidyl ethanolamine has a specific effect in accelerating the formation of clots in artificial blood systems.

As coronary thrombosis is usually associated with a demonstrable disturbance of lipid transport in the blood, these three observations, each relating some aspect of lipid transport with blood clotting or some component of its mechanism, are obviously of interest. For further details see Poole (1958).

NEFA (nonesterified fatty acids)

Chemists over 60 years ago reported that about 5 per cent. of the total fatty acids in blood was present in an unesterified form. This fraction was either dismissed as a chemical artefact or neglected completely. Only in the last 10 years, owing chiefly to the work of Dole (1958) and Gordon (1957), has its immense physiological importance been realised. NEFA is now known to be the form in which fat enters the blood from the storage depots in adipose tissue to serve as fuel for active muscle. In the blood it is carried bound to plasma albumin, one molecule of which can carry up to six molecules of NEFA. The usual concentration of NEFA in plasma is low (about 1 m-mole/*l.*) compared with that of glucose (about 5 m-mole/*l.*). However the rate of turnover is high and may be as much as 30 per cent. per min. This appears to be sufficient to supply the needs of an active man for calories.

The plasma NEFA is lowered when the rate of utilisation of glucose is increased, either by giving glucose by mouth or by insulin. It is raised when fat mobilisation is increased, for example during starvation or after giving pituitary growth hormone. It is also raised by adrenaline. In the first few minutes of exercise when fat utilisation exceeds fat mobilisation, plasma NEFA may fall. With prolonged exercise it rises unless there is a plentiful supply of carbohydrate as an alternative fuel.

As stated in Chapter 4 there appears to be considerable limitations to the rate at which alimentary glucose can be directly utilised.

Much of our basic knowledge about the factors regulating blood sugar were discovered by Claud Bernard just over 100 years ago. Bernard was able to make these discoveries because the chemist Fehling, who introduced the copper-reducing methods for estimating glucose, was contemporary with him in Paris. Whereas it is easy to measure blood sugar, satisfactory methods for measuring plasma NEFA were introduced less than 10 years ago. The procedure still requires considerable analytical skill. As Dole has pointed out, if it had been easy to measure NEFA and difficult to measure glucose, then the story of our knowledge of the body fuels would have unfolded very differently.

Alpha and beta lipoproteins

Although chylomicra and the NEFA-albumin complex are technically lipoproteins, this term is often used to refer to two classes of compounds in the plasma—the low density beta lipoproteins and the high density alpha lipoproteins.

Immense interest is now taken in the beta lipoproteins because their concentration in the plasma of patients with ischæmic heart disease is usually raised.

The lipoproteins are complex molecular aggregates in which the proportion of lipid to protein varies greatly. The lighter beta lipoproteins may contain as little as 7 per cent. of protein and only a small quantity of phospholipid, but they have large amounts of triglycerides. Most of the cholesterol present in plasma is in the beta lipoprotein fractions. The heavier alpha lipoproteins may contain up to 50 per cent. of protein ; most of the lipid is phospholipid with relatively little triglyceride.

These lipoproteins play a part in the transport of certain lipids, but for what purpose is not clear. Levels in the plasma remain relatively constant in any one individual and they are little affected by meals and everyday activity. They are not concerned with the transport of lipid either from the intestines after a meal or from the adipose tissue to muscle. Isotopic studies show turnover rates which are measured in hours or days (those for chylomicra and NEFA are in minutes). As Olson and Vester (1960) point out, it is difficult to tell which parts of the lipoproteins are vehicles for transporting the lipid and which are the cargo. Perhaps the high density lipoproteins can be considered as empty vehicles and the low density as vehicles loaded with cargo of triglycerides and cholesterol. There is evidence that the beta lipoproteins may be formed largely in the liver. Perhaps they act as vehicles carrying cargo for the maintenance of *l'élément constant* of lipids in the tissues, whereas chylomicra and NEFA are the forms of transport for *l'élément variable*. This is only speculation.

Lipoproteins can be separated by electrophoresis and also, on account of the differences in their densities, in an ultracentrifuge. The ultracentrifuge allows the amounts of the various fractions in the plasma to be accurately measured (Gofman *et al.*, 1954). The quantity of one fraction of the beta group (known as the Sf 12–20 fraction in the peculiar notation of the ultracentrifugers) is raised in most patients with ischæmic heart disease. The level of this fraction and the level of cholesterol in the plasma are closely associated. An ultracentrifuge is a costly instrument available in only a few laboratories. Nearly all European and most American workers consider that plasma cholesterol estimations reflect the level of beta lipoproteins sufficiently accurately for clinical and epidemiological studies of atherosclerosis and its clinical sequelæ.

Although the beta lipoproteins and cholesterol in the plasma remain relatively constant throughout the day, dietary, hormonal and many other factors can alter profoundly the level in any individual. However, it usually takes several days or even weeks for these changes to occur.

FACTORS AFFECTING THE LEVEL OF CHOLESTEROL IN THE PLASMA

Long-term dietary effects

The effect of diet on levels of plasma cholesterol has been investigated in two ways. First, there have been many epidemiological studies of levels of plasma cholesterol among people with very different dietary habits. Secondly, the effect of change of diet on cholesterol levels has been observed under controlled experimental conditions in human subjects.

In epidemiological studies Ancel Keys (Keys *et al.*, 1955) of the University of Minnesota has been a pioneer ; his results and general conclusions have now been confirmed in many countries. In brief, there is a marked difference in the levels of cholesterol among people in prosperous communities in the U.S.A. and Northern Europe compared with those in poorer communities in Southern Europe, Africa and Asia.

Plasma cholesterol levels are in part dependent on *age*, as shown by the data in Table 6, 1 which is based on analyses of sera from over 1000 apparently healthy New Yorkers. Many other studies in prosperous communities both in America and in Europe have given similar results, though the rise in levels with age is not always so high. By contrast in all studies in communities where there is much poverty, the rise in

TABLE 6, 1. *Serum cholesterol levels in health*

(Mean values mg./100 ml.)

Age Group (years)	Males	Females
3–7 . . .	180	209
8–12 . . .	180	196
13–17 . . .	176	183
18–22 . . .	185	193
23–27 . . .	195	202
28–32 . . .	243	200
33–37 . . .	231	207
38–42 . . .	247	225
43–47 . . .	237	239
48–52 . . .	239	250
53–57 . . .	240	286
58–62 . . .	236	267
63–67 . . .	249	260

Observations on over 1000 apparently healthy New Yorkers (Adlersberg *et al.*, 1956).

cholesterol with age either does not occur or is very small. An excellent example has been provided by Brock and his colleagues (Bronte-Stewart *et al.*, 1956) in Cape Town where, for men aged about 45 the mean level of plasma cholesterol is 234 mg./100 ml. in the European community and 166 mg./100 ml. in the Bantu.

There are many ways in which the life of prosperous people in the United States, Northern Europe and Cape Town differs from that of poor communities such as the Japanese and Bantus. One is that the former get about 40 per cent. of the total calories in their diet from fat, whereas the less prosperous get about 20 per cent. or less. That these levels of cholesterol in the blood in various communities are related to dietary habits is strongly suggested by experiments in which the cholesterol level in the blood of human volunteers has been greatly altered by dietary changes, as explained below.

In man, the total intake of dietary cholesterol has a negligible effect on plasma cholesterol levels. Even eating ten eggs a day (eggs are the only rich source of cholesterol in the human diet) does not usually raise the level of plasma cholesterol. However, the level can be altered by changing the fat intake in the diet. At first, the total amount of fat in the diet was thought to be the most important factor, since it was found experimentally that the plasma cholesterol levels could be raised or lowered (after an interval of several days) by raising or lowering the total amount of fat consumed.

A fresh approach to the problem was introduced when Kinsell and his colleagues (1952) in California showed that the plasma cholesterol was lowered when plant fats were substituted for animal fats in the diet. These observations have been extended by Ahrens and a group (1957) at the Rockefeller Institute in New York, by Beveridge and his colleagues

(1956) in Kingston, Ontario, Canada, and by Brock and his colleagues (Bronte-Stewart *et al.*, 1956) in Cape Town. The latter report that levels of serum cholesterol and of lipoprotein were reduced when olive oil, groundnut oil, sunflower-seed oil, arachis oil, seal or pilchard oil was given ; dripping, butter, chicken fat and hydrogenated groundnut oil raised the levels. In experiments carried out over many weeks on patients living on artificial diets with a single source of fat in the diet, the Rockefeller group have shown that minimal levels of cholesterol were obtained when the fat was provided by corn oil. Similar low levels were found with safflower oil, cotton-seed oil and peanut oil, but lard, palm oil, beef fat, butter and coconut oil raised the level. The fats with a high proportion of saturated fatty acids and a low iodine value raised the levels of cholesterol above those found with corn oil which has a high proportion of unsaturated fatty acids and a high iodine value.

Kinsell and others have always maintained that the essential fatty acids have a specific effect in lowering plasma cholesterol. This is strongly contested, notably by Ahrens, who considers that it is the overall degree of unsaturation of the fats in the diet, as judged by the iodine value, which determines the cholesterol level. Ahrens *et al.* (1959) found that corn oil (rich in EFA) was no more effective than oil from the fish menhaden, which is almost devoid of EFA.

These human experimental studies lend support to the hypothesis that the differences in levels of plasma cholesterol found in epidemiological studies can be attributed, in part at least, to differences in the quality of the fatty acids in the dietary fats. The full effect of a change of diet on the plasma cholesterol is usually apparent only after two weeks and persists for at least eight weeks. Whether the changes are permanent, when a new dietary habit is maintained, is not yet known.

The mechanism whereby unsaturated dietary fats lower the plasma cholesterol is not yet understood. In an investigation in Cape Town (Gordon *et al.*, 1957), sunflower-seed oil produced a marked fall in plasma cholesterol ; this was accompanied by a considerable increase of bile acids in the fæces. This suggests that the vegetable oil promoted the catabolism and excretion of cholesterol. It may be concerned with the reabsorption in the gut of endogenously produced cholesterol. A normal individual usually excretes about 1 g. daily of cholesterol in the bile. Part of this cholesterol is esterified in the lumen of the gut and reabsorbed, and a part is lost in the fæces in the form of coprosterol. The nature of the dietary fatty acids with which this endogenous cholesterol is esterified in the gut might have a decisive influence on the tendency of the body to reabsorb its own biliary cholesterol.

Other factors determining levels of plasma lipids

Hereditary.—There is a rare hereditary disease, idiopathic hypercholesteræmia, in which the patients have very high levels of plasma cholesterol. It is probable that this disease is transmitted by a gene which is incompletely dominant (Osborne *et al.*, 1959). It is possible that this gene is fairly common in many communities, but it is usually unable to penetrate (in the technical language of geneticists). Increasing age, dietary and other environmental factors may unmask its activities in some manner as yet not clearly understood. However this may be, it is certain that the members of some families have a greater liability than normal to developing raised plasma cholesterol levels.

Hormones.—The thyroid gland certainly exerts a marked effect on all plasma lipids. Much experimental and clinical evidence concur to show that thyroid hormones lower the level of plasma lipids. When the secretion of the hormone is deficient, as in myxœdema, all blood lipids—especially cholesterol—are increased. Similarly both in animals after pancreatectomy and in patients with uncontrolled diabetes mellitus, there is usually a marked hyperlipæmia and hypercholesterolæmia. The effects of the thyroid gland and pancreas on plasma lipids have been well known for several years. However, the mechanism by which the secretions of these glands exert these effects is little understood. Again, the effects have been studied for the most part in gross human disease and after severe experimental procedures in animals. Little is known of the influence, if any, of these glands in determining the extraordinary variability between different individuals in the levels of the plasma lipids. Oliver and Boyd (1958) have written a comprehensive review of the influence of hormones.

The sex hormones.—Table 6, 1 shows that there are important differences between the plasma cholesterol levels in the two sexes. When the sex glands are active, the level in women is lower than that in men. However, after the menopause there is usually a sharp rise. Oliver and Boyd (1953*a*) studied the variations that took place in the menstrual cycle in normal young women. They found a fall in the level of plasma cholesterol esters and a less marked fall in the level of phospholipids, both at the time of ovulation and just before menstruation. At these periods œstrogen secretion is probably at a maximum. During pregnancy there is usually a steady rise in the level of plasma cholesterol, which reaches a maximum at about the thirty-second week. Thereafter there is a decline, which continues slowly throughout the puerperium, though a slight secondary rise often occurs at the establishment of lactation. Œstrogens reduce the levels of plasma cholesterol in males with ischæmic heart disease ; substantial falls of as much as 30 mg./100 ml. occur in a few days. However, in many individuals the dose of œstrogen necessary to produce a significant fall in plasma cholesterol also caused undesirable secondary effects such as gynæcomastia and loss of libido, and made no difference to the incidence of recurrent attacks of infarction in a carefully controlled clinical experiment (Oliver & Boyd, 1961).

Physical exercise.—The effect of physical work and exercise on blood lipids has received some study. It has been suggested that the rise in plasma cholesterol found in prosperous communities may be due in part to the sedentary life that is commonly led. There is some evidence consistent with this view. Thus a study in Boston (Mann *et al.*, 1955) showed that the rise in cholesterol associated with a high intake of saturated fats could be prevented in young men if they took hard and regular physical exercise. In Finland (Karvonen *et al.*, 1958) the cholesterol levels were measured in 44 men aged 21 to 38 who had been training for a ski-ing competition. The mean value was 204 mg./100 ml., which was 25 mg. less than the mean value for a group of men of comparable age.

Shaper *et al.* (1961) studied nomadic tribesmen in Africa. These men drink up to 10 pints of milk a day and so have a diet rich in fats which might be expected to raise the plasma cholesterol levels. Yet the mean level was 166 mg./100 ml., a very low figure judged by American or European standards. The large amount of exercise which these men take following their herds of cattle may be responsible for keeping their plasma cholesterol at a low level.

The subject is still under discussion. A statement which would probably be widely acceptable is : physical exercise may play a part in determining the level of plasma lipids, but, if so, it is a much less important factor than the quality of the dietary fats.

The blockage of cholesterol synthesis.—Endogenous production of cholesterol takes place in the body, probably in the liver. There are drugs which can inhibit this process. One of these, triparanol (Mer-29) has been given by Oaks *et al.* (1959) to 36 patients with serum cholesterol levels over 250 mg./100 ml. In all but 4 there was a substantial decline in the level. This substance has now been shown to be dangerously toxic, but other preparations may be developed in the future which may be of great clinical value.

Comment.—' Blood cholesterol ' is a subject which is ' news.' This is because of its undoubted association with atherosclerosis and its sequel, ischæmic heart disease (Chapter 40). Like all other ' news ' its clinical importance has at times been exaggerated and distorted in newspapers, on television and on the radio. Consequently a word of warning may not be inappropriate. The chemical estimation of plasma cholesterol is a convenient way of measuring blood beta lipoproteins, the metabolic functions of which are not yet established. It is known that a number of factors determine their level in the blood, but the relative importance of these factors is disputed. Although much has been learned about cholesterol and lipoproteins in the last 15 years, much more information must be acquired before their role in health and disease can be clearly stated.

ADIPOSE TISSUE

Old textbooks of physiology dismissed adipose tissue briefly as an inert store in which the surplus energy of diet was kept in the form of fat until needed. Two Israeli scientists in a classical review (Wertheimer

& Shapiro, 1948) were mainly responsible for dispelling this idea and demonstrating that adipose tissue has considerable metabolic potentialities. It is now known, largely due to turnover studies with isotopes and to investigations *in vitro*, that adipose tissue is capable of a great variety of chemical reactions. Glucose can be converted into glycogen and into fat, and it is also oxidised. Glucose uptake and oxidation in adipose tissue is markedly increased by insulin (Winegrad & Renold, 1958). Indeed when its metabolism is expressed on a fat-free basis or per unit of nitrogen present, adipose tissue appears as chemically active as most other organs. Human adipose tissue usually contains 80 to 90 per cent. of fat, the remainder being cells and supporting tissue. The normal human has some 10 kg. or more of adipose tissue, which will have a fat-free active mass of the order of 1 kg. Brozek and Grande (1955) have attempted to partition the basal metabolism of man amongst the different organs of the body, based on data for oxygen uptake of individual organs. The liver, kidneys, brain, heart and muscle account for 87 per cent. This leaves 13 per cent. for other organs, of which by far the largest is adipose tissue. They may well have over-estimated basal oxygen consumption of muscle and, if so, the remainder attributable to adipose tissue will be higher. Anyhow, it accounts for a significant amount of the basal metabolism. Adipose tissue is no inert substance.

The store of fat is maintained from the dietary intake. It is filled up or depleted, depending on the balance between the energy value of the food eaten and the energy value of the physical exercise taken by each individual. It is obvious that the size of the store varies remarkably from one individual to another. What determines this size and by what mechanism does an individual gradually increase or reduce the size of his or her store ? Can the adipose tissue send a chemical signal to the appetite centres informing it of the size of its fat reserves ? The answers to these questions may be found in the factors that regulate appetite (Chapter 3).

Fat mobilisation.—As already stated, fat is liberated from the depots into the blood in the form of NEFA. There have been many studies of factors which may influence this and these have recently been reviewed (Fritz, 1961). Adrenaline certainly promotes a rapid release of NEFA and growth hormone is also a fat-mobilising agent, though its action takes hours in man, whereas adrenaline operates in minutes. Several other fat-mobilising factors have been described and there is one which has been demonstrated by Chalmers *et al.* (1960) in human urine during starvation, though it has not yet been chemically identified.

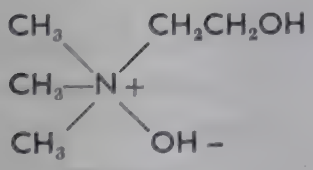
Distribution of adipose tissue.—Male connoisseurs of the female form are reputed to start their visual inspection at the ankle and work upwards. This traditional guide is generally reliable. But sometimes the amount of subcutaneous fat over the ankles and legs bears little relation to the amount of fat elsewhere. This is perhaps a relatively common but minor manifestation of the process responsible for the rare disease lipodystrophy, in which the fat disappears from the face, arms and legs and accumulates around the hips and thighs.

As middle-age advances, especially in the male, many people acquire a greatly increased layer of fat over the abdomen and at the same time their limbs become thin. For the present it is perhaps sufficient to say that subcutaneous fat is an ‘ organ ’ of which little is known and which merits more study both by clinicians and research workers.

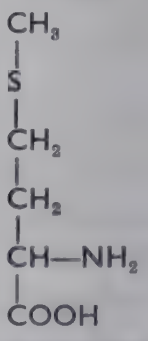
DIET AND LIVER FAT

Fat in the liver.—The liver normally contains only 5 to 7 per cent. of fat (wet weight) : this fat cannot be seen under the microscope. In various dietary circumstances and as a result of poisons or disease, the amount of fat in the liver may be increased enormously. As much as 70 per cent. of its weight may be fat and in extreme cases the histological appearance may at first glance resemble subcutaneous adipose tissue. The liver has a reputation as the ‘ chemical workshop ’ of the body ; certainly it has a high turnover rate for fats. It also usually contains fatty acids, which are more unsaturated than the fatty acids in the adipose tissues. The conversion of the mixed fats present in a diet into the fat that is specific for the species takes place mostly in the liver. There also, carbohydrate can be converted into fat and fats perhaps converted into carbohydrate. Formerly the liver was considered by far the most important if not the only site for these reactions ; but, as already mentioned, adipose tissue has been shown to have chemical potentialities of its own and nowadays it would appear that few such reactions occur exclusively in the liver.

Lipotropic factors.—Before the discovery of insulin, patients with diabetes frequently had large fatty livers. Soon afterwards the Toronto School discovered that fatty livers developed in depancreatised dogs maintained on insulin for a long time. Best and his colleagues have developed these observations and shown that dietary factors play a large part in controlling the fat content of the liver (Best & Taylor, 1961). There are a number of substances that are capable of preventing this accumulation of fat. Of these the most important appears to be the base, choline. However, choline is not an essential dietary substance ; it can be synthesised in the body and so should not be classed as a vitamin.



Choline



$$CH_3-S-CH_2-CH_2-CH(NH_2)-COOH$$

Methionine

For this synthesis a suitable source of methyl (CH_3) radicles is necessary and these can be supplied by the amino acid methionine or by betaine or from other dietary sources. These substances contain a labile methyl group which becomes available in the body for the synthesis of choline.

Most foods of animal origin are good sources of choline and most animal proteins contain useful amounts of methionine. Caseinogen in milk is one of the best. Foods of vegetable origin generally contain much less both of choline and methionine than animal foods. As choline is not the only ' lipotropic factor ' controlling liver fat, and as it can be synthesised by the body (provided the necessary labile methyl groups are available), it is impossible to state accurately the dietary requirements for choline, even in experimental animals, much less in man. Mixed diets contain good amounts, but poor vegetarian diets do not. A fatty liver is an essential feature of kwashiorkor, the disease which is so common in African and Asiatic children who are weaned on poor vegetarian diets (Chapter 28). The fatty livers associated with alcoholism are perhaps caused by a deficiency of lipotropic factors resulting from a poor food intake rather than to any direct toxic effect of alcohol.

EFFECTS OF DEFICIENCY OF FAT

Burr and Burr (1929) first showed that certain fatty acids (EFA) were essential in the diet for the health and survival of rats. Their results have been fully confirmed and a great deal is now known about the pathological consequences of this deficiency in the rat. When young rats are put on a fat-free diet immediately after weaning, they continue to grow normally for two or three weeks. The rate of growth then declines and usually stops within 8 to 10 weeks. During this period an eczematous scaliness of the skin develops. This is most marked over the tail, but the paws are also severely affected and no part of the skin is altogether spared. This can be prevented by giving cotton-seed oil or EFA. Rats cannot synthesise these acids, but they can convert one into another. Arachidonic acid is probably the physiologically active form, but both linoleic and linolenic acid are readily converted to it in the body so that either alone can prevent the signs of deficiency. Vitamin B_6 (pyridoxine) is probably needed for the conversion. If hydrogenated coconut oil is added to the diet, the eczema develops sooner and growth ceases earlier. The need for EFA may thus be inversely related to the amount of saturated fatty acids in the diet. The male rat needs about four or five times as much as the female for rapid growth.

Evidence of this deficiency, similar to that found in rats, has been produced in mice and dogs. Calves, pigs and poultry have also been reported to be susceptible to the deficiency, although in these species it is not so readily produced. A variety of insects have been shown to require ' essential fatty acids.' There is thus good reason to suppose that they are needed by all animal tissues.

However, there is so far no good clinical evidence that man ever lacks a sufficient dietary source of EFA. Certainly these acids are likely to be needed for the nutrition of the individual cell, but it is probable that these needs are small, perhaps only 1 g./day, which is supplied by the poorest of diets. It is now over 30 years since Burr and Burr first announced their discovery ; in that time clinicians have searched through the whole gamut of clinical medicine for the human counterpart of scaly tails in rats. Hansen and his colleagues (1958) for many years have claimed that certain forms of eczema in children on low fat diets based on skimmed milk respond to EFA therapy. This condition must be very rare and experience has shown that large doses of unsaturated fat give no benefit to most luckless infants with eczema.

After the discovery by Kinsell that dietary EFA could lower raised plasma cholesterol levels, it was natural to speculate that EFA deficiency was responsible for the disturbance of fat transport causing these raised levels. Sinclair (1956) has postulated that EFA deficiency is common in modern prosperous communities and contributes to the production of degenerative disease, especially of the arterial wall. This view has received much publicity, but little experimental support. A strong point in Sinclair's argument is that cholesterol in the plasma is preferentially esterified with EFA and that when cholesterol is esterified with *unnaturally* saturated fatty acids it is disposed of less readily. Yet Bothcher and his colleagues (1960) who have analysed human atheromatous material have found that with increasing severity of the disease there is an *increasing* percentage of linoleic acid in the cholesterol-ester fatty acids. Thus there appears to be no lack of EFA in this disease. The best that can be said for Sinclair's hypothesis is the old Scottish verdict : ' not proven.'

Satisfactory scientific proof that EFA deficiency exists in man is still lacking. One human volunteer remained for six months on a fat-free diet without developing any skin disorder (Brown *et al.*, 1938). This fits in with the experience among the Hos in India, as described in the next section.

DIETARY NEEDS FOR FAT

The amount of fat in the diets in different countries varies greatly (Table 6, 2). It is very difficult to state what represents too much or too little fat for health. However, in all civilisations, Eastern or Western, old or new, fat has always been an important necessity for the preparation of good meals. There is almost no country where a housewife can prepare the meals which she would like for her family without materials in which fat supplies at least 20 per cent. of the calories. That the average figure in several countries is far below this, reflects the wide incidence of poverty. Many people cannot enjoy their traditional diet through lack of fat. In Great Britain, for several years before the last war, fat provided 39 per cent. of the total calories in the diet. As a result of war-time rationing and restrictions on food this figure fell gradually and reached a

TABLE 6, 2. *Approximate percentage of dietary calories supplied from total fats in the period* 1951-53

Country	Cal. from fat	Country	Cal. from fat
	Per cent.		Per cent.
Japan	8	Greece	24
South Africa (Bantus)	10	France	30
India	13	Holland	34
Turkey	14	United Kingdom	35
Brazil	18	Australia	38
Portugal	20	Sweden	38
Italy	20	Canada	38
Spain	22	U.S.A.	41

Compiled by Keys from FAO sources.

minimum of 33 per cent. in 1947. Thereafter it rose steadily and, by 1954, it was back to 39 per cent. This small war-time restriction of the fat intake caused much publicly voiced discontent. Many of the ailments of the time were ascribed to a shortage of fat in the diet, not only by harassed housewives but also by some responsible physicians. A national diet containing 33 per cent. of fat certainly supplies far more fat than is necessary to meet physiological needs. Hence no conceivable physical harm could have arisen from this restriction. Nevertheless there was much discontent. In retrospect it seems clear that the true explanation of this discontent was that many articles of food cooked with inadequate amounts of fat are insipid and unpalatable to traditional British tastes. In any country social requirements for fat for ' good living ' are far higher than physiological requirements for physical health. In the present state of knowledge it is quite impossible to state a minimum fat requirement for man.

Human diets low in fats are almost always also low in protein and other nutrients necessary for the maintenance of health. It is thus very difficult to ascribe any disease arising in these conditions specifically to a deficiency of fat. (This statement requires qualification because of the vitamins present in some fats, but the body has alternative sources of the fat-soluble vitamins, as described in Chapter 13.)

Minimal requirements for fat may indeed be very low. Mitra (1942) has made an interesting study of the dietary habits of the Hos, an aboriginal tribe in the Bihar Province of India. He investigated 250 families and found that 200 made no use of any kind of fat in their cooking. This was not due to poverty, for many of the Hos had acquired some money by collecting forest products and they visited bazaars in nearby towns where they could have purchased fats had they so wished. They did not do so because they were ignorant of the use of fats and oils in cooking ; their culinary practices were limited to boiling and—very occasionally—baking. The Hos possess cattle but use them only as beasts of burden ;

they collect no milk and eat no meat. The total daily fat intake of different families was estimated as varying from 2·4 to 3·8 g./head/day, which would provide at most 2 per cent. of the total calories, but might contain 1 g. or so of EFA. Although the health and nutrition of these aborigines were by no means ideal, they presented no signs or symptoms which could be attributed to fat deficiency ; their general level of nutrition and physique was no worse than that of neighbouring villagers who regularly consumed vegetable oils.

High fat diets are almost always also high in calories and so—except in those physically active—lead to obesity. High fat diets are also associated with disturbances in the fat transport mechanism as already described and this may be a factor contributing to a variety of diseases. But again, this effect may be due to an adverse ratio of saturated to unsaturated fatty acids in the diet rather than to the total amount of fat.

Practical Recommendations

Although scientific precision is lacking for making such recommendations, two seem sensible. First, any community which wishes to feed well and in a civilised tradition (either Eastern or Western) must obtain at least 20 per cent. of its calories from fat. Secondly, individuals in prosperous communities who lead *sedentary lives* and have reached *middle-age* would be well advised to limit their fat intake to 25 to 30 per cent. of their total calories. The importance of reducing intakes of animal fats and the use of vegetable oils in the prevention and treatment of atherosclerosis is discussed in Chapter 40.

A high fat intake is essential for very active people spending over 4000 Cal./day. Lumberjacks in the sub-Arctic and workers on polar expeditions often require this amount of energy and would have to devote much of their working day eating to obtain such a high caloric intake solely from bulky carbohydrate sources. Fats give them the necessary energy quickly, so that they can get on with their job in the short time allotted to them.

CHAPTER 7

ALCOHOL

THE alcohol in alcoholic drinks can be utilised by man as a source of energy. Chronic alcoholics may obtain a large proportion of their daily caloric requirements from this source. In some countries, especially those with a large wine-growing industry, alcohol may provide up to 10 per cent. of the total national supply of calories.

Pure ethyl alcohol (ethanol, C_2H_5OH) when combusted in a bomb calorimeter yields 7·1 Cal./g. When alcohol is given to man, either by mouth or injection, it is eliminated from the body at about 100 mg./kg./hr., mostly by oxidation. There is considerable variation in the rates found for different individuals, but almost all fall within the range 60 to 200 mg./kg./hr. Very little is excreted either through the lungs or the kidneys. The latter have little or no power to concentrate alcohol. The rates of excretion by the lungs and kidneys are directly proportional to the concentration of alcohol in the blood and to the volumes of air expired and of urine excreted. With a blood alcohol concentration of 100 mg./100 ml. (a level normally associated with symptoms of intoxication) and a ventilation rate of 10 *l.*/min. (the normal value when sitting) the excretion of alcohol in the breath is about 4 mg./kg./hr. During a period when the blood alcohol is declining from 100 mg./100 ml. to zero, with a urine output of 1 *l.* during this period, the average elimination of alcohol through the kidneys is about 1·5 mg./kg./hr. (Lundsgaard, 1953). Thus out of an average elimination rate of 100 mg./kg./hr. only about 5 per cent. would be excreted through the lungs and kidneys and over 90 per cent. of the alcohol would be oxidised.

In experiments in the calorimeter chamber, Atwater and Benedict (1902) showed that the energy liberated by the oxidation of alcohol can be utilised by the human body and can replace isocaloric quantities of carbohydrate and fat. The amount of alcohol which can act as a source of metabolic energy in a given time is independent of the concentration in the blood. The oxidation is not accompanied by any increase in the basal metabolic rate (*i.e.* there is no specific dynamic action). In rats, alcohol can contribute only up to 50 per cent. of the basal metabolism ; in man the figure may be a little higher than this and up to 65 per cent. of the basal metabolism. The rate of utilisation cannot be increased by muscular exercise or by exposure to cold. Most of the oxidation of alcohol probably takes place in the liver, where it is oxidised in preference to other nutrients including protein. Under suitable circumstances alcohol has been shown to promote growth in rats. Useful reviews of the physiological behaviour of alcohol have been given by Le Breton and Trémolières (1955) and Trémolières and Carré (1959).

When alcohol is taken in small quantities it undoubtedly acts as a food. For practical purposes its caloric value in a diet can be taken as 7 Cal./g. The average rate of elimination of alcohol (100 mg./kg./hr.) in a 65 kg. man corresponds to the metabolism of about 160 g. of alcohol in 24 hours with a total energy value of about 1100 Cal. This amount of alcohol would be obtained from about 2 *l.* of wine, 7 pints of beer or 16 oz. of spirit. There is little reason to doubt that the alcohol in alcoholic drinks can be utilised as a source of energy up to these amounts by many people. It must be emphasised that these are average figures. In some subjects the maximum rate of elimination is only 60 mg./kg./hr. This figure forms the basis for the poster that the visitor to Paris may see on the Metro : "*Les prescriptions de l'Académie de Médecine* ; *jamais plus d'un litre de vin par jour !*"

Such formidable intakes of drink are well below the amounts that may be consumed regularly by a few chronic alcoholics and occasionally by others on a spree. Most people cannot increase their rate of alcohol elimination, nor is there any evidence of an increased rate in chronic alcoholics ; if they take part in a heavy drinking bout the excess alcohol remains in the body fluids and will be slowly but steadily oxidised : several days may elapse before the blood is cleared of alcohol. In wine-growing countries there is a small proportion of people who regularly take more than 2 *l.* of wine daily. Jellinek (1955) presents data suggesting that up to 1 per cent. of adult Italian males may be in this category. Both in Italy and France it is well known that some men drink steadily from before breakfast till bedtime. Few chronic alcoholics will give a truthful account of their daily consumption ; but anyone who admits to taking an alcoholic drink before breakfast, 'just to start the day right,' will almost certainly end the day having taken too much for his health. Such men may consume regularly 3 *l.* of wine each day. This will contain at least 250 g. of alcohol. Such a high intake will be associated with constant high levels in the blood and a consequent increased excretion through the lungs and kidneys. However, it is doubtful whether this excretion can ever be much more than 10 per cent. of the intake. Just how heavy drinkers dispose of such large quantities of alcohol is not yet fully understood.

All alcoholic drinks contain some carbohydrates but little or no protein. Heavy drinkers can thus get a high caloric intake from wine or spirits alone. If their appetite remains good they often become obese. But many alcoholics consume very small amounts of other foods, especially those rich in protein. Indeed the protein content of the diets of even moderate drinkers is usually low. It is probable that this protein deficiency is mainly responsible for the liver disorders which are so common in chronic alcoholics. Vitamin deficiency diseases are also frequently found in association with chronic alcoholism for the same reason. Rats and mice, given free access to alcohol, have been shown to consume more when the supply of thiamine and other vitamins of the B group is diminished (Mardones, 1951). This presumably is an adaptation to the fact that alcohol is oxidised without the need for the carboxylase enzyme system, which is dependent on thiamine. Thus a deficiency of the B group of vitamins may lead to a high intake of alcohol which in turn may further reduce the vitamin consumption. In some human chronic alcoholics a vicious circle of this nature may perhaps be present. Alcoholism has often been a social problem among poor rice-eating people with a low level of thiamine intake.

Ethyl alcohol in dilute solution (6 per cent.) can be given intravenously. It has been used to supplement amino acids and glucose in the treatment of severe malnutrition, associated generally with surgical conditions of the alimentary tract (p. 685).

In the past it has often been the custom to omit the calories provided by alcoholic drinks in computing national caloric intakes. There seems to be little physiological justification for this custom though it has been followed by the Food and Agriculture Organisation (FAO) of the United Nations. Data supplied by H.M. Customs and Excise show that during 1953-54 alcohol in alcoholic drinks provided about 74 Cal./day/head of adult population in the United Kingdom. In addition 25 Cal./day might be provided by other nutrients in the drinks, *e.g.* sugars in beer. There is little information as to how these calories are distributed throughout the population.

CHAPTER 8

NUCLEIC ACIDS

NUCLEIC acids are found in all animal and plant cells and are therefore present in primary foodstuffs, though absent in secondary products such as refined sugar and separated fats. They have been known to man for nearly 100 years, since Miescher first isolated material rich in them from the nuclei of pus cells and later from the sperm heads of Rhine salmon. Their general chemical composition has been known for many years, but it is only in the last 20 years that the structural organisation of their molecules has been elucidated and their great biological importance realised. The simple nucleotides, which contain the vitamins nicotinamide and riboflavin, act as essential respiratory co-enzymes (Chapter 9). The two most important polynucleotides or nucleic acids are ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), which control the synthesis of proteins in the cells. DNA is confined to the cell nucleus and forms the genes of the chromosomes, through which heredity is controlled.

A very full account of nucleic acids is given in a monograph by Chargaff and Davidson (1960). Davidson (1960) has also written a smaller monograph. A modern account of the biosynthesis of proteins is given by Chantrenne (1961).

CHEMISTRY AND BIOCHEMISTRY

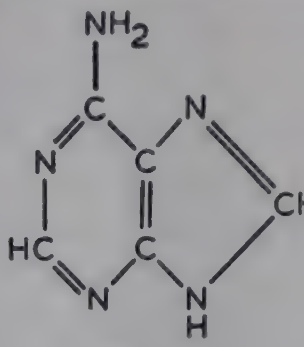
Nucleic acids are complex molecules built up of many individual units known as *nucleotides*, all of which have the same essential structure, namely :

Organic base—Pentose sugar—Inorganic phosphate

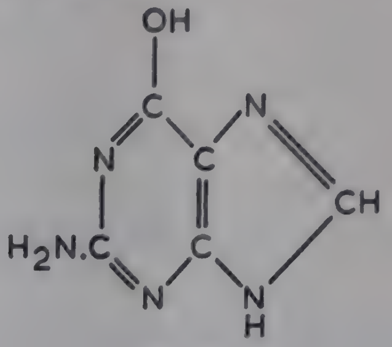
The nucleic acids are divided into two different classes according to the nature of the pentose sugar that forms the essential link in their nucleotides. In the ribonucleic acids (RNA) the sugar is ribose ; they are found in the mitochondria, nucleolus and general cytoplasm of the cells. In the deoxyribonucleic acids (DNA), on the other hand, the sugar is deoxyribose : they are found within the nucleus and are the essential part of the chromatin material.

The nature of the bases concerned is a matter of special interest. In most nucleic acids they consist of equal parts of purines and pyrimidines.

The two purine bases that occur in all nucleic acids are adenine and guanine. Their structural formulæ are as follows :

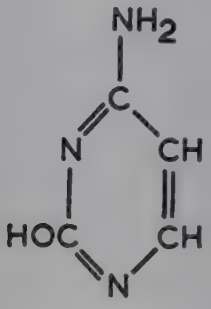


adenine

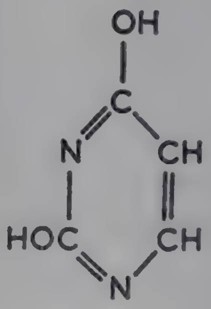


guanine

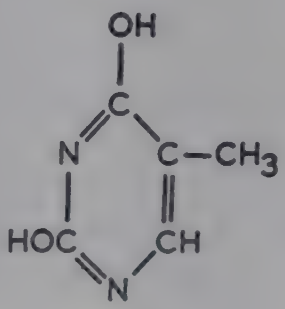
There is one pyrimidine that is constantly present in all nucleic acids, namely cytosine. The RNA of the cellular cytoplasm contains also the pyrimidine uracil, whereas the DNA of the nucleus contains instead thymine.



cytosine

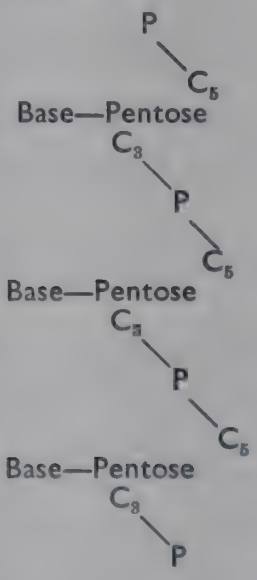


uracil



thymine

The nucleotides are linked together through the phosphate radicle to form chains known as polynucleotides. Each phosphate radicle is attached to the C_3 carbon atom in the pentose of one nucleotide and to the C_5 carbon in the pentose of the next, thus :



The structures of complex molecules can be investigated by studying the path taken by X-rays passing through them. By such methods it has been possible to demonstrate that the molecule of DNA consists of two chains of polynucleotides, each in the form of a right-handed helix and each coiled round the same axis. Crick and Watson (1954) have proposed a model of these helices, a modification of which is shown in Fig. 8, 1. In this model the phosphate groups are on the outside of the helix and the purine and pyrimidine bases lie inside the helix at right angles to its long axis. The two helices are held together by hydrogen bonds which link the bases. But the bases can only be linked in specific pairs :

adenine with thymine,
guanine with cytosine.

The order in which the bases occur in any one helix can be infinitely varied and so permits the existence of an infinite variety of nucleic acids. Fig. 8, 1 gives an indication of what may happen in the chromosomes when a cell divides : the two helices would break apart and separate ; each can then reconstitute the original. Because of the specific pairings of the bases, it might be expected that each helix would build up on itself (from the free bases, pentose and phosphate in the neighbourhood) a second helix which would be identical with the original from which it had become separated. Thus each strand of the double helix acts as a pattern or template for the building of a new polynucleotide chain, ensuring that the new double helix synthesised is always precisely identical with the original. It is now certain that DNA is a principal chemical component of the chromosomes which carry the genes determining hereditary characteristics. This model provides a possible explanation of the chemical processes whereby the genes are reconstituted by chemical synthesis after each cell division. The model and the template analogy must be oversimplifications, but there is much chemical and X-ray evidence consistent with the view that biological synthesis can proceed in some such manner.

Ribonucleic acids may have a similar role in the cytoplasm to DNA in the nucleus, in this case concerned with the synthesis of proteins. The phosphorus atoms in a nucleic acid molecule are separated from each other by a distance which is very similar to the distance between peptide bonds in a polypeptide chain. Brachet, who himself has contributed much to this subject, reviewed 274 papers in his article in Chargaff and Davidson's monograph and concludes that " the work of recent years has considerably strengthened the hypothesis that RNA plays a role in protein synthesis ; but however convincing, the evidence still remains circumstantial."

The molecular weights of the nucleic acids have proved difficult to determine. DNAs are certainly very large molecules with molecular weights of the order of 1,000,000 (corresponding to some 2000 to 3000 nucleotides). RNAs are not so large ; most estimations of their molecular weight are of the order of 10,000. Nucleic acids are usually found in nature linked with a protein to form nucleoproteins. The proteins with

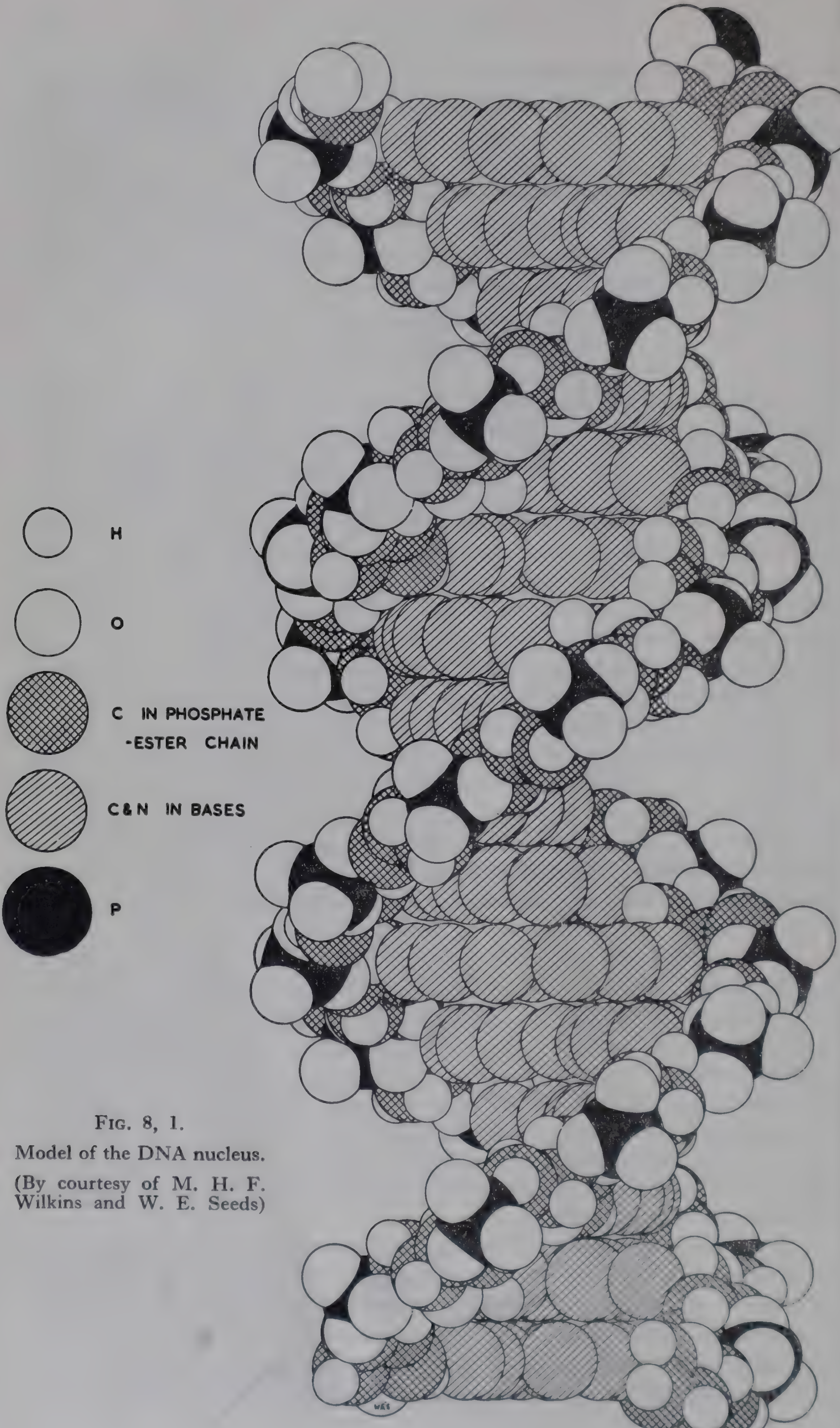


Fig. 8, 1.
Model of the DNA nucleus.
(By courtesy of M. H. F. Wilkins and W. E. Seeds)

which they are combined are relatively simple histones and protamines with a lower molecular weight than DNA.

The absolute amount of DNA in the tissues of any organ remains remarkably constant, whether the state of nutrition of the individual is good or bad ; it appears to be independent of changes in the weight of the whole organ. This is because DNA is the chief component of the stable chromosomes in the cell nuclei. By contrast, the absolute amounts of RNA in any tissue is variable and associated with its total protein content. The amount of DNA in a tissue can be used as a chemical measure of the number of cells present. This has proved of practical value in a number of recent experimental metabolic and nutritional studies, especially of the liver.

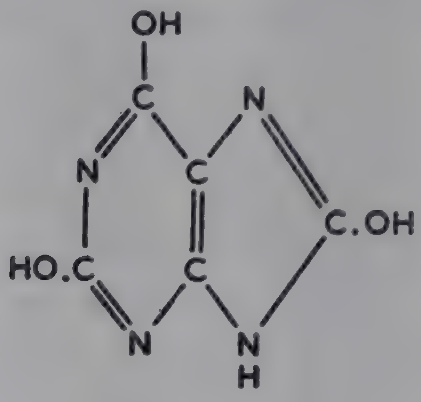
Of particular interest to nutritionists is the fact that in some nucleotides the base has proved to be a vitamin ; for instance both riboflavin and nicotinic acid are now known to exert their metabolic role by virtue of their position in particular nucleotides which are essential components of certain specific enzymes. This is further discussed in Chapter 9. It is now established that cyanocobalamin (vitamin B_{12}) is a nucleotide linked to a porphyrin-like ring ; this opens up a whole new field of possible relationships between nucleic acid metabolism and the maturation of red blood corpuscles and other cells.

METABOLISM OF NUCLEIC ACIDS

Studies using isotopic nitrogen (^{15}N) have shown that the human body is capable of synthesising for itself the nucleotides which go to make the nucleic acids from the simplest of raw materials derived from the breakdown products of proteins, fats and carbohydrates. The only exception is in the case of those nucleotides which include a vitamin in their structure ; their successful synthesis requires a dietary supply of the vitamin as a necessary raw material.

In the course of the wear and tear of cellular metabolism, and perhaps particularly when the nucleus disintegrates and reassembles in the process of cell division, some nucleic acids are thrown out from the cell and are destroyed. The molecules of which they are made are disposed of in various ways ; the pentose sugars are probably oxidised on the spot to carbon dioxide and water ; the phosphoric acid enters the general metabolic pool of inorganic phosphate and, after supplying any immediate need for phosphate elsewhere in the body, the remainder is excreted, chiefly in the urine. Little is known of the catabolic fate of the pyrimidine bases ; they are probably converted into urea and carbon dioxide and excreted as such. The purines on the other hand are resistant to catabolism in the tissues : although they undergo some oxidation, their essential structure is not disrupted thereby ; they are converted into uric acid.

Uric acid.—This acid has been recognised for many years as one of the regular constituents of human urine. Its chemical composition is as follows :



uric acid

In some animals (notably the birds and reptiles) uric acid is the principal form in which excess nitrogen is excreted in the urine. By contrast mammals excrete nitrogen mainly in the form of urea. The uric acid that is always present in normal human urine is derived from the catabolism of purines. These purines originate in part from the body's own cells wherein they were first synthesised, and in part from the cellular material of the diet. A small amount of uric acid is constantly present in the blood and in certain diseases the amount is increased, notably in chronic failure of the kidneys and in gout. The presence of a raised blood uric acid in gout is an important clue to the nature of that disease, which is further discussed in Chapter 43.

Chapter 9

THE NUTRITION OF THE CELL

INTERMEDIARY METABOLISM AND BIOLOGICAL OXIDATIONS

AFTER considering the dietary origin and metabolic fate of carbohydrates, proteins and fats, and reviewing briefly the fundamental role of the nucleic acids in living processes, it is appropriate now to consider how the individual cells in the human body are nourished. This is not an easy subject to discuss, because inevitably it involves some highly technical knowledge of biochemistry. Doctors and dietitians whose aim is to give their patients sound advice on the choice of food in the prevention and treatment of disease may find this chapter difficult, especially if they graduated some years ago before the recent spectacular advances in biochemistry. For their benefit we have attempted, in the following pages, to summarise the principal features of cellular metabolism in simple language. Readers with a good background of chemical knowledge, and particularly professional biochemists, may consider that this review has oversimplified an extremely complicated subject. Our reason for writing this chapter is because we believe that, if science is to serve the nutritional requirements of man, it is most important that nutritionists should have a general understanding of the ideas of the cellular physiologist, and *vice versa.*

The fundamental processes of nutrition take place in the cells—processes for which all practical dietetics must cater. The various chemical mechanisms described in this chapter have, for the most part, been elucidated by a study of the behaviour of isolated fragments of tissues suspended in dilute solutions of salts and sometimes nutrients. The introduction of radioactive isotopes and the tracer techniques has greatly accelerated the rate of discovery of metabolic pathways. It can be argued that the chemical behaviour of isolated fragments of dying tissue has little relation to what is happening in the whole living body and that there is no proof that reactions demonstrated *in vitro* actually take place *in vivo*; but this is a specious argument, based on half-truths. Certainly there is seldom direct evidence that reactions demonstrated *in vitro* are, in fact, taking place within the living body. Yet, without involving teleological considerations, it is difficult to conceive that the many pieces of chemical machinery that have been demonstrated to exist in isolated tissues play no part in normal biological behaviour. It is almost certain that all the enzymic processes known to biochemistry play some part in the nutrition of the cell, even though the actual behaviour of living matter is probably more complicated than the mechanisms described in the most advanced biochemical textbooks. Biochemists, like other biologists, tend to oversimplify and so perhaps to overemphasise the biological importance of each new chemical discovery. It is probable that cells are never dependent on only one method for carrying out each of their essential metabolic processes. Alternative chemical means are usually available. For instance, the effect on the body of a diet deficient in thiamine, an essential part of the mechanism for the breakdown of carbohydrate, depends in part on other components of the diet. These may enable other enzymic reactions to compensate to some extent for a failure of those dependent on thiamine. Precise knowledge of the relative importance to life of different enzyme systems is seldom available, though it is safe to say that probably none are unimportant.

Most biochemical studies have been concerned with the enzymic breakdown of complex substances into simpler ones. Much less is known about biological synthesis. All enzymic reactions are at least partially reversible, and synthetic processes may sometimes proceed backwards along the same lines as degradation processes. The possible role of nucleic acids in the synthesis of proteins has been mentioned in Chapter 8. However, conditions essential for intracellular synthesis are very imperfectly understood. A brief, preliminary summary of the principal features of cell metabolism, all of which are now well established, may assist an understanding of the details.

1. The chemical energy present in the food and the body stores first becomes available to the cells in the form of glucose, fatty acids and amino acids, which are transported to the cells in the blood and extracellular fluid.
2. This chemical energy is released by oxidative processes within the cells. These processes take place in a series of stages which take *time*.
3. For many living processes—such as muscular contraction—chemical energy has to be made available very *rapidly*. (The unit of time used by muscle and nerve physiologists is one thousandth of a second.) Several organic substances, notably adenosine and creatine, form esters with inorganic phosphoric acid. Large amounts of energy are stored in the ‘ energy-rich ’ bonds, which link the phosphoric acid with these substances. These bonds can be broken down very rapidly by hydrolysis and provide the *immediate* source of energy for vital activity.
4. The energy liberated more slowly by the oxidation of nutrients is utilised to reform the organic phosphate compounds and so recharge them with ‘ energy-rich ’ bonds.
5. Glucose, fatty acids and some amino acids are broken down in the cells to fragments containing two carbon atoms. These two carbon fragments contain most of the chemical energy originally present in the nutrient.
6. The fragments combine with an organic substance known as coenzyme A to form acetyl-coenzyme A. Coenzyme A contains the vitamin pantothenic acid (p. 248). Acetyl-coenzyme A can be oxidised in the cells with conversion of the carbon atoms into carbon dioxide, the liberation

of energy and the formation of free coenzyme A again. This oxidation with liberation of energy takes place in a series of stages known as the tricarboxylic or Krebs cycle.

7. Acetyl-coenzyme A is a starting material for the synthesis of new carbohydrate, fat and protein in the body. It is thus a key stage in the interconversion of the energy-yielding nutrients.

8. Oxidation can take place in the cell in three ways: (1) by the addition of oxygen to a molecule, (2) by the removal of hydrogen from a molecule and (3) by the loss of an electron, as when ferrous iron is oxidised to ferric iron.

9. Five vitamins (thiamine, nicotinic acid, riboflavin, pantothenic acid and pyroxidine) each form a part of the molecule of five coenzymes, responsible for five enzymic processes in the above reactions. The body is dependent on an adequate supply of these vitamins to enable these essential enzymic reactions to proceed. More is said about this in Chapter 14.

‘ ENERGY-RICH ’ PHOSPHATE ESTERS

Muscles require an immediate source of energy if they are to contract quickly. The chemical energy in glucose and other nutrients in the cell can only be liberated by breakdown processes, which require a long sequence of enzymic reactions. The immediate source of energy necessary for muscular movement is provided by ‘ energy-rich ’ phosphate esters. Of these by far the most important is adenosine triphosphate (ATP). One phosphate radicle can be liberated from a molecule of ATP very rapidly, thereby setting free a large amount of energy (about 7 Calories per gram molecule). At the same time the ATP molecule is converted to adenosine diphosphoric acid (ADP), which must then be recharged by the addition of another phosphate radicle. ATP is universally distributed in living cells. There is now much evidence that it plays a fundamental, if not unique, role in supplying the energy, not only for the muscles but also for all activities of every organ and tissue. Several other ‘ energy-rich ’ phosphate esters may be present in the cells, notably creatine-phosphate (phosphagen) in muscles. Possibly their main role is the immediate recharging of ADP to ATP by means of the energy held in their phosphate bonds.

Ultimately the preservation of adequate amounts of ATP in the cells depends on the supply of energy in the nutrients and on inorganic phosphates. It is well known that some muscular work can be carried out anaerobically. It is possible, for instance (though rare in practice), for a sprinter to run 100 yards without breathing. Yet the muscles and all other tissues are ultimately dependent on the energy liberated from the oxidation of nutrients by the oxygen inspired through the lungs.

When muscles are working anaerobically, glucose or glycogen are broken down to lactic acid, which accumulates in the body. When 1 molecule of glucose is converted into 2 molecules of lactic acid, sufficient energy is liberated to build up 2 ATP molecules from ADP by combination with 2 phosphate radicles. But most of the chemical energy present in the glucose remains in the lactic acid. If oxygen then becomes available, lactic acid is broken down completely to CO_2 and water. In this process 1 molecule of lactic acid provides sufficient energy to recharge 18 molecules of ATP. One molecule of glucose, if completely oxidised, can thus recharge $2+18+18=38$ molecules of ATP ; in this way energy to the value of $38 \times 7=266$ Calories can be transferred to ATP from 1 g. molecule of glucose. In Chapter 2 it was stated that 1 g. of carbohydrate yielded about 4 large Cal. on complete combustion. The calorific value of glucose is a little lower than this overall figure (3·69 Cal./g.). The molecular weight of glucose is 180. Therefore 1 g. molecular weight of glucose on complete combustion yields in all $180 \times 3{\cdot}69=664$ Calories. Of this amount, about 266 can be transferred to the 'energy-rich' phosphate bond in ATP and so made available immediately for muscular work or other vital activity. The efficiency of this transfer is thus about 40 per cent., which is high for any thermodynamic process.

It will have been noted that only a very small proportion of the total energy in glucose can be liberated anaerobically. The greater part is liberated by oxidative processes which will now be considered.

An excellent and full account of energy transformation in living matter is given by Krebs and Kornberg (1957).

BIOLOGICAL OXIDATIONS

Acetyl coenzyme A

It is now established that glucose, fatty acids and some amino acids are all broken down in the cell to a 2-carbon acetate ($CH_3.CO$—) fragment. This contains most of the energy present in the original molecules ; it is the oxidation of this fragment that provides most of the energy for biological processes. Before oxidation, the 2-carbon acetate fragment must be joined to coenzyme A and this compound—acetyl coenzyme A—is of immense importance. Its discovery by F. Lipmann of New York in 1945 has been rewarded with a Nobel Prize. First, acetyl coenzyme A is the common channel into which most of the carbon atoms from carbohydrates, fats and many proteins go before ultimate oxidation. Secondly, it is probably the primary building stone for the synthesis of those proteins, fats and carbohydrates which comprise the essential structure of the body and also those that make up its stores. Thirdly, by virtue of its key position, it is a link both in the formation and in the breakdown of acetoacetic acid and other 'ketone bodies,' which are so important in diabetes mellitus and other metabolic disorders of man.

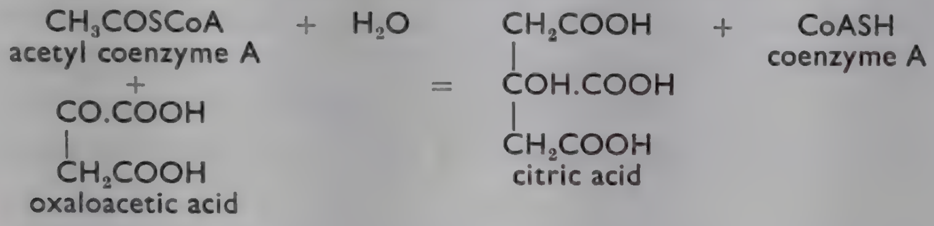
The chemical structure of coenzyme A has been determined ; the molecule is now known to be composed of three portions, made up of a molecule each of ATP, pantothenic acid and β-mercapto-ethanolamine linked together. Pantothenic acid is a vitamin, deficiency of which produces well-defined signs in experimental animals (p. 248); whether a deficiency ever arises in man is, as yet, unknown. β-mercapto-ethanolamine has a sulphidryl radicle (—SH) at the end of the molecule. Coenzyme A can therefore exist in two forms, the reduced form CoASH and the oxidised form CoAS-SCoA, in the same manner as the sulphur-containing amino acids and glutathione. Coenzyme A is linked with acetic acid through the —SH group.

$$CH_3COOH + CoASH = CH_3COSCoA + H_2O$$

The method by which acetyl coenzyme A is oxidised will be considered first, and subsequently the manner of its formation from hexoses, amino acids and fatty acids.

The tricarboxylic or Krebs cycle

Acetyl coenzyme A reacts with oxaloacetic acid to form the tricarboxylic acid—citric acid—and at the same time coenzyme A is set free. Thus:

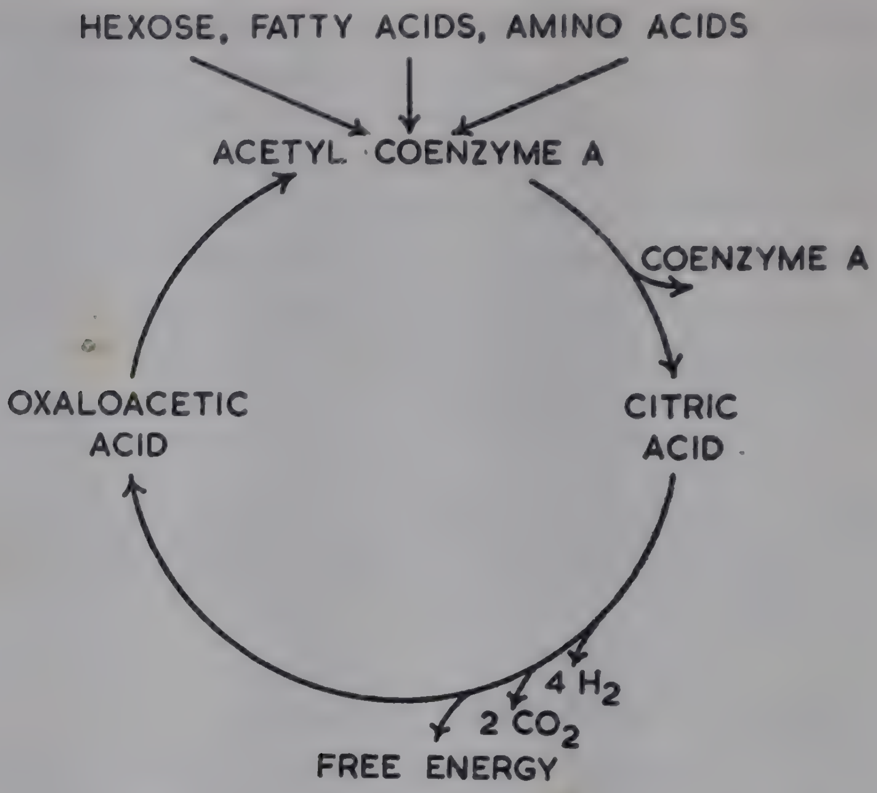


$$\begin{array}{ccccccc} \underset{\text{acetyl coenzyme A}}{CH_3COSCoA} & + & H_2O & & CH_2COOH & + & \underset{\text{coenzyme A}}{CoASH} \\ + & & & & | & & \\ CO.COOH & & & = & COH.COOH & & \\ | & & & & | & & \\ \underset{\text{oxaloacetic acid}}{CH_2COOH} & & & & \underset{\text{citric acid}}{CH_2COOH} & & \end{array}$$

Citric acid is then converted back into oxaloacetic acid by a series of enzymatic processes involving seven intermediary stages. In the course of these stages, the original citric acid molecule gains 2 molecules of water but loses 4 molecules of hydrogen and 2 molecules of CO_2. The chemical energy present in the original 2-carbon acetate fragment is set free. The processes are represented in the diagram shown on page 128.

The oxaloacetic acid molecule which is reformed is free to unite with another molecule of acetyl coenzyme A, to form citric acid once more. In this way the cycle is repeated. This mechanism, whereby successive molecules of acetyl coenzyme A can set free the chemical energy in the original nutrients, is known as the tricarboxylic acid or Krebs cycle. Krebs is a distinguished Nobel prize-winner, who is now Professor of Biochemistry at Oxford.

The practical importance of the Krebs cycle in animal life is well illustrated by the story of Gifblaar poisoning: a full account has been given by Peters, (1949). In 1944 Marais reported that many sheep and cattle in South Africa had died as a result of eating a plant known as Gifblaar. The botanical name of the plant is *Dichapetalum cymosum.* Marais showed that the toxic principle in the plant was fluoroacetic acid ($CH_2F.COOH$). Subsequently it was shown that the poisonous effect of fluoroacetate is attributable to the fact that it blocks the Krebs cycle immediately after the formation of citric acid. In animals poisoned



with fluoroacetate, the tricarboxylic cycle is blocked and so citric acid accumulates ; the concentration of the acid in the organs may be ten to fifty times that found in the organs of control animals (Table 9, 1). Fluoroacetate poisoning thus shows that the Krebs cycle operates *in vivo*.

TABLE 9, 1. *Effect of fluoroacetate upon accumulation of citrate in the rat*

Citric acid μg./g. wet tissue.

Tissue	Control	Poisoned	Increase
Blood . . .	3·0	50	16 times
Liver . . .	0·8	31	40 times
Brain . . .	21·0	166	8 times
Heart . . .	25·0	677	26 times
Kidney . . .	14·0	1036	56 times

Data from Peters (1949).

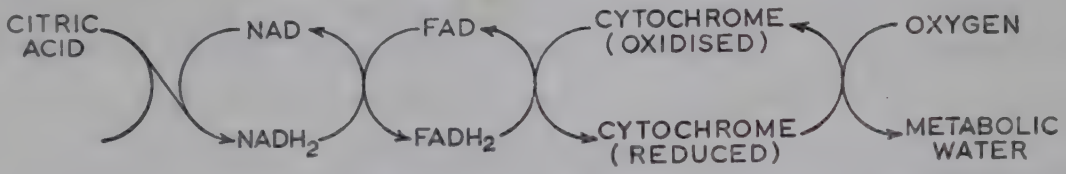
In medical practice, fluoroacetate appears to have been used, so far, only by certain witch-doctors in Sierra Leone. They found a plant allied to *Dichapetalum cymosium* an effective remedy for relieving their clients of troubles caused by objectionable enemies. How a plant manages to synthesise fluoroacetate and how it acts in the plant are two unsolved problems. Whether small amounts of fluoroacetate may be present (but hitherto undetected) in other botanical species is unknown. It is important to remember that clinical conditions exist, associated with a poor diet, but which yet are not attributable to deficiency of any known nutrient. The possibility that some of these are due to hitherto unidentified poisons in plant foods which interrupt intermediary metabolism has not yet been adequately explored. This subject is further discussed in Chapter 25.

To return to the main theme, it will have been noticed that molecular oxygen plays no part in the Krebs cycle. The oxidative processes are effected by the removal of hydrogen which is then transferred to a series of carriers, before oxidation by molecular oxygen is possible.

THE MECHANISMS OF CELLULAR OXIDATION

Oxidative processes involving the removal of hydrogen can only take place in the presence of an enzyme belonging to the class of dehydrogenases. More than thirty such dehydrogenases have been described. They enable hydrogen to be transferred from a substrate to a carrier, which is then reduced.

The dehydrogenase system responsible for the oxidations of the Krebs cycle involves three intermediary carriers before molecular oxygen effects the final conversion of the hydrogen to water. They can be represented diagrammatically thus :



where NAD stands for the oxidised form of nicotinamide-adenine dinucleotide * and FAD for the oxidised form of flavin-adenine dinucleotide. Thus the hydrogen from the Krebs cycle is picked up by NAD and $NADH_2$ formed. This is then at once oxidised and passes the hydrogen on the FAD. The $FADH_2$ formed is again quickly oxidised. A hydrogen molecule from $FADH_2$ reacts with 2 molecules of oxidised cytochrome (which contains Fe^{+++}). Two electrons are transferred to the cytochrome molecules, which reduce Fe^{+++} to Fe^{++}. At the same time 2 hydrogen ions ($2H^+$) are formed. Molecular oxygen then is able to take up the 2 electrons from the reduced cytochrome (thereby oxidising it) and with these electrons and the hydrogen ions forms metabolic water. Thus oxygen takes part only in the final phase of the chain of oxidative processes.

The intermediary carriers must now be considered. NAD has the constitution :

$$\underbrace{\text{nicotinamide—ribose—phosphoric acid}}_{\text{pyridine nucleotide}} \text{ — } \underbrace{\text{phosphoric acid—ribose—adenine}}_{\text{adenylic acid}}$$

---

* For many years this coenzyme was known as diphosphopyridine-nucleotide or more familiarly DPN. This name is inaccurate and the International Union of Biochemists has recommended it be no longer used.

It can accept hydrogen at a double bond attached to the pyridine ring in the nicotinamide molecule (p. 229) to form reduced $NADH_2$. This nicotinamide portion of the molecule is derived from the vitamin nicotinic acid. There is now no doubt that the principal role of this vitamin in the body is as a component for the synthesis of NAD.

FAD is a coenzyme, which has the constitution :

$$\underbrace{\text{riboflavin—phosphoric acid}}_{\text{flavin nucleotide}} \text{ — } \underbrace{\text{phosphoric acid—ribose—adenine}}_{\text{adenylic acid}}$$

FAD can accept hydrogen at the double bonds on the 2 nitrogen atoms in the riboflavin molecule (p. 233) and is then converted into the reduced $FADH_2$. The vitamin riboflavin is thus an essential part of the FAD molecule which, like NAD, has the structure of a dinucleotide (Chapter 8).

NAD and FAD are most important typical members of two classes of coenzymes which act as hydrogen carriers. There are other coenzymes with similar activities and also similar chemical structures ; they will be found described in textbooks of biochemistry.

Cytochrome.—There are at least three cytochromes which are very widely distributable in all living tissue. The molecule of each consists of four pyrrole rings united to form a porphyrin ring similar in structure to the porphyrin ring in hæmoglobin. At the centre of the molecule is an atom of iron loosely attached to each pyrrole ring. This atom can exist in the ferrous and ferric forms. The oxidation of the ferrous to the ferric form is brought about by an enzyme, cytochrome oxidase, in the presence of oxygen. This is the final stage in most oxidative processes in mammalian tissues. As with NAD and FAD, the business part of the cytochrome molecule—that part which is oxidised and reduced—is an essential dietary nutrient. Iron, nicotinic acid and riboflavin are thus essential nutrients, each of which has a specific role in biological oxidations.

The foregoing simplified account of one important sequence of biological oxidations is presented to explain the essential parts played by iron, nicotinic acid and riboflavin in the tissues. Brief mention must now be made of three other substances which undoubtedly play an important but as yet ill-defined role in biological oxidations. These are ascorbic acid, glutathione and vitamin E.

Ascorbic acid (p. 214) is very readily oxidised to dehydro-ascorbic acid—a process that is easily reversible. It would seem very unlikely that the role of ascorbic acid in the tissues is not in some way related to this—its most characteristic chemical property. The biological properties of ascorbic acid are discussed in Chapter 14. So far, it has not been possible to correlate these properties with any specific role in a particular enzyme system. This is in contrast to most of the other water-soluble vitamins which have a well-defined place in the enzymic reactions of the cells.

Glutathione is a tripeptide with a sulphydryl group which can be easily converted from the reduced —SH to the oxidised —S—S— form.

Like ascorbic acid, it is widely distributed in the tissues. It may act as a hydrogen carrier for enzyme systems, but no specific role has as yet been discovered. A possible action of glutathione is that of keeping ascorbic acid reduced. Even if this is so, its significance is not understood.

Vitamin E (p. 210) consists of a group of substances—the tocopherols—which are powerful anti-oxidants. It would seem probable that this characteristic chemical property is related in some way to the control of energy utilisation in the cells. So far, however, attempts to demonstrate this have met with little success.

The precise roles of ascorbic acid, glutathione and vitamin E in biological oxidations remain at the moment important but unsolved problems.

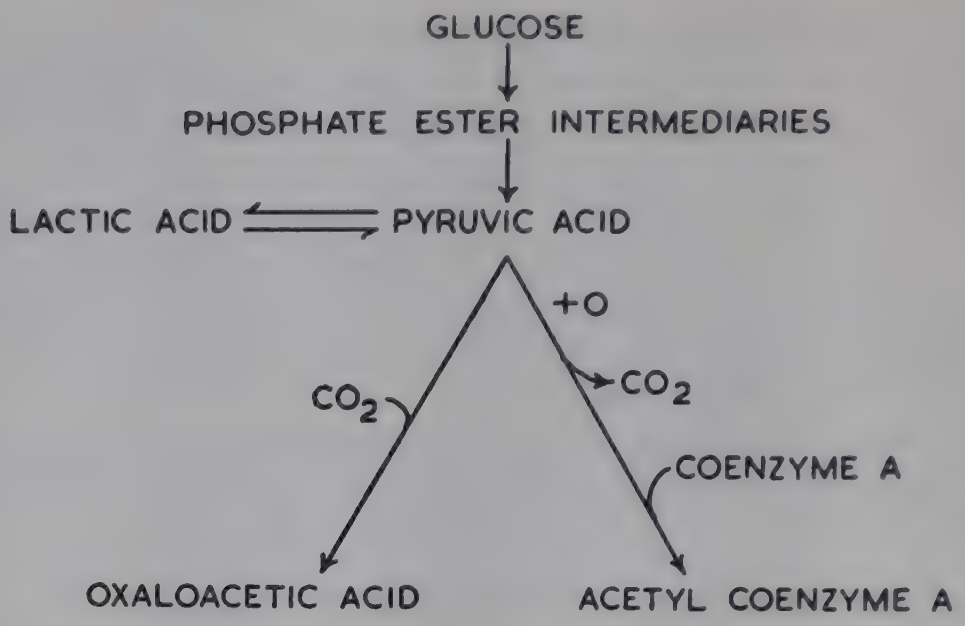
INTERMEDIARY METABOLISM OF GLUCOSE

It is now time to return to the consideration of some of the intermediary stages in the breakdown of hexoses, fatty acids and amino acids, and the formation from them of acetyl coenzyme A. In the breakdown of glucose a key stage is the formation of pyruvic acid ($CH_3COCOOH$). The conversion of glucose into pyruvic acid initially involves the formation of two esters of glucose with phosphoric acid (the first containing one and the second two phosphate radicles, both phosphate radicles being supplied by ATP). The hexose-diphosphate breaks down into 2 molecules of triose-phosphate from which 2 molecules of pyruvic acid are formed.

In the absence of an adequate supply of oxygen, pyruvic acid is reduced to lactic acid ($CH_3CHOHCOOH$). During anaerobic work, lactic acid accumulates in the muscles and diffuses out into the blood and extracellular fluid. When a free supply of oxygen becomes available, lactic acid is oxidised back to pyruvic acid; the pyruvic acid molecule then loses the —CO group (*i.e.* undergoes oxidative decarboxylation) and forms acetic acid which links with coenzyme A to form acetyl coenzyme A, which then enters the Krebs cycle. These changes can be represented as shown in the diagram on page 132.

Under certain circumstances pyruvic acid appears to be able to enter the Krebs cycle by an alternative route. It takes up a molecule of CO_2 and then forms the 4-carbon compound, oxaloacetic acid.

The great interest of these changes to nutritionists is that thiamine is part of the coenzyme responsible for the oxidative removal of the –CO radicle (decarboxylation) from pyruvic acid. In the absence of a dietary source of thiamine, cocarboxylase cannot be manufactured, and supplies run out. Pyruvic acid then accumulates in the tissues and this biochemical lesion is responsible for the clinical features associated with thiamine deficiency (Chapter 32). Before thiamine can act as a coenzyme, it must be phosphorylated; cocarboxylase is thiamine pyrophosphate. Historically this was the first demonstration of the precise mode of action of a vitamin in cellular metabolism. The credit for the initiation of this important work



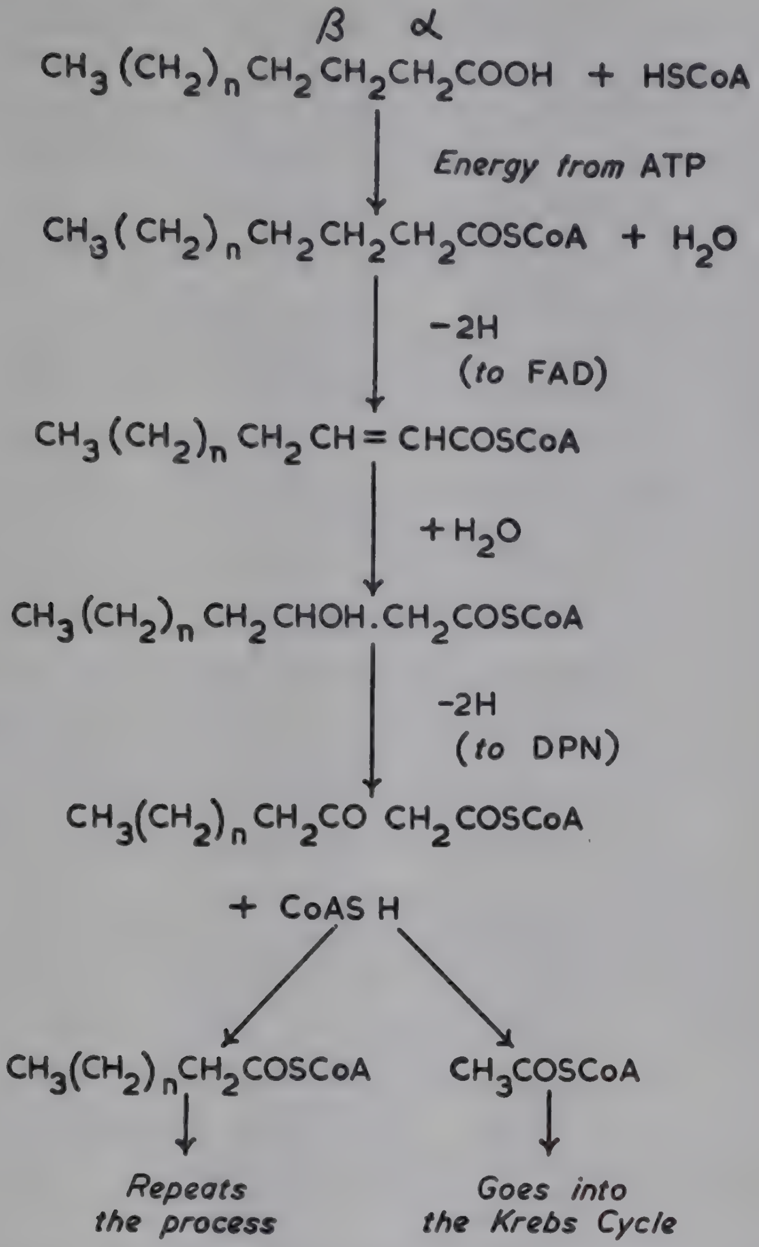
goes to Sir Rudolph Peters, who coined the useful phrase ' biochemical lesion ' at the time.

Intermediary Metabolism of Fatty Acids

It has long been known that the fatty acid chain can be broken down in the body by a series of oxidations, each of which removes a 2-carbon fragment (β oxidation). Largely owing to the brilliant work of the German physiologist Lynen, it is now known how this is brought about. Again coenzyme A plays an essential role. The process may be represented as shown in the diagram on page 133.

The fatty acid molecule combines with a molecule of coenzyme A. For this reaction energy is required, which is supplied by ATP. The fatty acid coenzyme A compound is reduced in three stages and an oxygen atom attached to the β carbon atom. FAD and NAD act as hydrogen carriers for the necessary removal of hydrogen. The fatty acid chain now has acetoacetyl coenzyme A formed at the end. This can react with another molecule of coenzyme A and the molecule then splits at the β position. The 2-carbon fragment is acetyl coenzyme A which can go into the Krebs cycle. The remaining portion of the molecule is a fatty acid coenzyme A compound with two carbon atoms less than at the start. This compound then goes through the same stages as before and two more carbon atoms are broken off to form another molecule of acetyl coenzyme A. The process is then repeated until the fatty acid is finally broken down. Molecules of acetyl coenzyme A are thus produced in numbers equal to half the number of carbon atoms in the original fatty acid and all of these can be oxidised in the Krebs cycle. Most of the chemical energy in the fatty acids is probably thus liberated through the Krebs cycle.

The last stage in the breakdown of a fatty acid is acetoacetyl coenzyme A ($CH_3CO.CH_2CO.SCoA$). Acetoacetic acid is the parent substance of the ketone bodies which are formed in the tissues in diabetes and other


β α
CH3 (CH2)n CH2 CH2 CH2 COOH + HSCoA
Energy from ATP
CH3 (CH2)n CH2 CH2 CH2 COSCoA + H2O
-2H
(to FAD)
CH3 (CH2)n CH2 CH = CHCOSCoA
+H2O
CH3 (CH2)n CH2 CHOH.CH2 COSCoA
-2H
(to DPN)
CH3(CH2)n CH2CO CH2 COSCoA
+ CoAS H
CH3(CH2)n CH2 COSCoA
CH3COSCoA
Repeats the process
Goes into the Krebs Cycle

metabolic disorders. It is now possible to consider what is known about the mechanism of their production.

Ketosis.—Three substances (ketone bodies) appear in the blood and urine in ketosis ; these are acetoacetic acid (CH_3COCH_2COOH), acetone (CH_3COCH_3) and β-hydroxybutyric acid ($CH_3CHOHCH_2COOH$). The latter of course is not strictly a ketone. Acetoacetic acid is certainly the parent substance from which both acetone and β-hydroxybutyric acid are formed ; the first by a simple chemical breakdown and the second by enzymatic reduction. β-hydroxybutyric acid is a much weaker acid than acetoacetic acid and thus causes less disturbance of acid-base balance.

All the ketone bodies can be readily oxidised in muscle where they may act as a valuable reserve fuel. Many studies have shown that the blood in the veins coming from a limb contains less acetoacetic acid than the arterial blood. Ketosis arises from an excessive production of acetoacetic acid in the liver. When acetoacetyl coenzyme A is formed in the liver it has three possible fates : (1) it can be oxidised to oxaloacetic acid and so pass into the Krebs cycle and be utilised as a source of energy ; (2) it can be hydrogenated and then utilised as material for the synthesis of fat ; or (3) it can be hydrolysed, in which case the free acetoacetic acid may escape into the blood, producing ketosis.

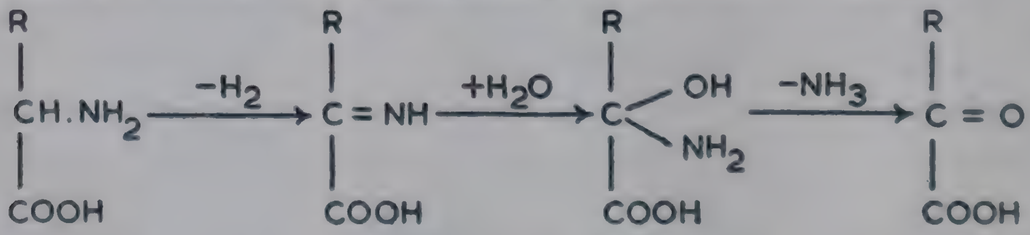
Lipmann (1954) has pointed out that in the liver there is a fine balance between the catabolic, anabolic and hydrolytic enzymes which compete for the disposal of the acetoacetyl coenzyme A molecule. Ketosis results when the balance is tipped in favour of the hydrolytic process.

In practice it appears that a certain proportion of carbohydrate is necessary in the metabolic mixture which is being oxidised in order to prevent ketosis. In uncontrolled diabetes, in starvation and when very low calorie diets are prescribed, carbohydrate utilisation is greatly reduced. Provided 15 per cent. or more of the calories utilised are derived from carbohydrate (as can be demonstrated by an R.Q. of 0·75 or above), ketosis does not occur. When less carbohydrate is being utilised and the R.Q. is below 0·75, ketosis is generally present, *e.g.* in the case of ketotic diabetic patients. However, there is considerable variation in the ease with which diabetics become ketotic and also in the degree of ketosis found in fasting healthy subjects. Obesity is usually associated with some degree of failure to develop ketosis during starvation ; many fat people do not become ketotic, even when apparently no carbohydrate is being metabolised as indicated by an R.Q. as low as 0·70.

How carbohydrate utilisation protects a person against excessive hydrolysis of acetoacetyl coenzyme A in the liver is unknown. Nor is it clear how some fat people manage to remain free from ketosis in circumstances under which thin people would have high levels of acetoacetic acid in the blood. The factors regulating acetoacetic acid formation remain an important and practical field for future study. Under certain circumstances both adrenocortical and pituitary hormones may regulate the process. Recent reviews of both physiological (Passmore, 1961*a*) and biochemical (Krebs, 1961) aspects of ketosis are available.

Intermediary Metabolism of Amino Acids

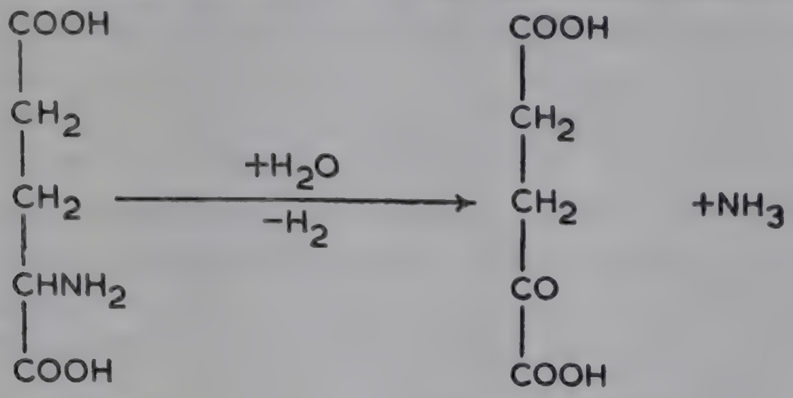
A most important process in the metabolism of all amino acids is the removal of the amino group and its replacement by oxygen with the formation of a keto acid. This reaction can be represented thus :



The ammonia formed can be subsequently built up into urea. The fate of the keto acids so formed is uncertain. It is probable that many of them undergo oxidative decarboxylation in the same manner as pyruvic acid with the formation of acetyl coenzyme A, which can of course be used for the synthesis of fat and carbohydrate or as a source of energy.

This is probably the normal mechanism whereby protein can be converted into carbohydrate or fat.

Certain amino acids can enter the Krebs cycle by an alternative route. Glutamic acid on oxidative deamination yields α-ketoglutaric acid thus :



$$\mathrm{HOOC{-}CH_2{-}CH_2{-}CHNH_2{-}COOH} \xrightarrow[-H_2]{+H_2O} \mathrm{HOOC{-}CH_2{-}CH_2{-}CO{-}COOH} + NH_3$$

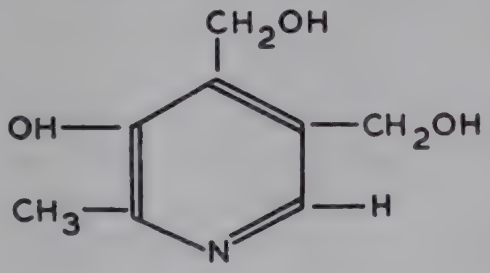
glutamic acid α-ketoglutaric acid

α-ketoglutaric acid is one of the intermediary stages between citric acid and oxaloacetic acid in the Krebs cycle.

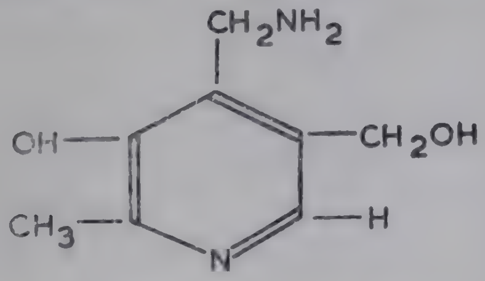
Transamination is a process whereby an amino group can be transferred to a keto acid in this general manner :—

$$R_1CH(NH_2).COOH + R_2CO.COOH \longrightarrow R_1CO.COOH + R_2CH(NH_2)COOH.$$

In this way new amino acids can be formed for the synthesis of new proteins. Transamination is of special interest because the vitamin pyridoxine acts as a coenzyme for the system. Pyroxidine has the structure :



and can take up the amino group from an amino acid to form pyridoxamine :



Pyridoxamine can then transfer the amino group to another keto acid. Studies with ^{15}N have shown that transamination is a frequent occurrence in the body, especially from glutamic to other amino acids.

COMMENT

There is now no reason to doubt that most of the energy present in the foods is made available to the body in the manner described above.

Thirty years ago these processes were almost entirely unknown: now they are part of established knowledge. Although alternative pathways for the breakdown of nutrients and the utilisation of energy certainly exist (*e.g.* the pentose phosphate shunt for the breakdown of glucose), their relative importance and the circumstances under which they are utilised are little understood. Five vitamins are known to be components of specific enzyme systems; yet it does not follow that the list is now closed and knowledge of this subject complete. It may well be that new research will show that other enzyme systems contain components which can only be provided in the diet and that new vitamins will be discovered. This is a possibility that does not seem to us to be remote. If this is admitted, certain points of practical food policy emerge and these are discussed in Chapter 17.

CHAPTER 10

WATER AND ELECTROLYTES

THE body of a 65 kg. man contains approximately 40 *l.* of water: of this about 25 *l.* is within the cells and about 15 *l.* in the extracellular fluids. The principal ions in the cell water are K and PO_4 and in the extracellular fluids Na and Cl. The membrane which surrounds the cell is permeable to water and to each of these ions. The maintenance of the different concentrations of ions on each side of the cell membrane is one of the most fundamental processes in biology. These ionic gradients can only be preserved by the expenditure of energy. Whenever a muscle or nerve is active, there is a change in the electrolyte equilibrium at the cell membrane and Na enters the cell. During the recovery processes—both of muscle and nerve—this sodium is pumped out of the cell and the original unstable equilibrium restored.

The normal concentrations of ions, both in the intracellular and extracellular fluids, is preserved by a balance between the intake of water and electrolytes in the diet and the output in the excretions. Disturbances of this balance are of great importance in clinical practice. Within the last 15 years there have been rapid advances in knowledge of electrolyte disturbances in disease. This has been due in no small part to the development of a rapid method of analysis, using the flame photometer. Sodium imparts a yellow colour to a flame, and potassium a violet colour. If a solution containing either of these elements is vaporised and the vapour passed through a gas flame, the intensity of the colour imparted to the flame can be measured photo-electrically, when other colours have been excluded by a filter. This intensity is quantitatively related to the concentration of each element in the original solution. By this method the Na and K concentrations in small quantities of biological materials can be measured quickly and accurately. The older chemical methods of determination involved much time and considerable analytical skill. This is an example of an important sequence—advance in analytical technique→ new physiological knowledge→fresh clinical understanding. Radioactive tracer techniques have also greatly facilitated studies of electrolyte distribution.

WATER

The water intake comprises the fluid drunk and the water in the food eaten. The water formed by the oxidation of carbohydrate, protein and fat is also available (metabolic water). The output consists of the urine, the water in the fæces and the water evaporated from the skin and lungs. Table 10, 1 shows a normal water balance in a young man leading a sedentary life.

TABLE 10, 1. *The daily water balance of a young man leading a sedentar life on a diet providing* 2110 *Cal./day* (Passmore, *et al.*, 1955*a*)

(Mean of five daily measurements)

		ml./day
Intake :	Water content of solid food	1115
	Liquid drunk	1180
	Metabolic water	279
		2574
Output :	Urine	1295
	Fæcal water	56
	Evaporative water loss	1214
		2565
Water balance		+9

It will be seen that the water and other fluids drunk are approximately equal to the urine output. It is this fact that makes the 'fluid balance chart'—which can be kept by the nursing staff in a ward—a useful practical procedure. It is particularly valuable in the routine care of febrile patients in the tropics, who are liable to become dehydrated unless carefully supervised.

THE DETERMINATION OF THE WATER BALANCE

For research purposes, if the facilities of a metabolic ward are available, the complete water balance can be determined. This may provide valuable information.

The fluid consumed is easily measured and the water in the solid components of the diet can be estimated by homogenising and drying an aliquot portion of a duplicate sample of the whole day's food.

The metabolic water can be calculated, since the oxidation of the proximate principles yields water in the following amounts :

1 g. starch yields 0·60 g. water.
1 g. protein yields 0·41 g. water.
1 g. fat yields 1·07 g. water.

If the subject is neither losing nor gaining weight, the composition of the diet provides a measure of the nutrients actually oxidised. If the subject is losing weight, an addition must be made for the water produced by the oxidation of tissue protein and fat : conversely, if the subject is gaining weight, the excess nutrients laid down do not yield water. The metabolic water is usually small in proportion to the total intake of water and any error will be of little significance in calculating the water balance.

The urine volume is easily measured, as is the fæcal water by weighing the fæces before and after drying. The evaporative water loss is determined from the invisible weight loss.

The invisible weight loss = weight of food and liquid consumed ± any change in body weight − the weight of urine and fæces.

These are all simple measurements.

The evaporative water loss = the invisible weight loss − weight of CO_2 expired + weight of O_2 absorbed.

Under normal circumstances the evaporative water loss is about 93 per cent. of the invisible weight loss. The exact figure depends on the R.Q. and may vary from 90 to 102 per cent.

PHYSIOLOGICAL VARIATIONS IN THE INTAKE AND OUTPUT OF WATER

Fluid intake

In normal life the intake of fluids is largely determined by social custom and habit. The kidney is the principal organ regulating the amount of water in the body. Thirst is normally an additional physiological regulating mechanism. It was at one time thought that thirst was produced by dryness of the mouth and throat. More probably the sensation of thirst arises as a result of a concentration of the sodium in the blood. An increase of 1 per cent. in the osmolarity of the blood causes thirst. The sensory receptors for thirst are in the hypothalamus and the thirst centre is closely connected with the appetite centres (p. 37). Thirst is predominantly associated with water depletion, but not with salt depletion. Indeed if there is an associated salt depletion such as may occur in the tropics as a result of losses in the sweat, the thirst mechanism may not operate adequately. For this reason men doing heavy manual work, and also febrile patients, may easily become dehydrated and salt depleted without complaining of thirst. Such people may have to be persuaded to drink sufficient water, to which salt has been added.

In medical practice fluids can be given in other ways than by mouth, *e.g.* into the veins, subcutaneously or into the peritoneal cavity.

Fluid output

Output from the skin.—Water is commonly lost from the skin by sweating. Rates as high as 2500 ml./hr. have been recorded in hot climates, both in the tropics and in hot industrial occupations. A loss of 500 ml./hr. is not uncommon. Unless this water is replaced by an increased intake, the body will become dehydrated. Severe symptoms result from dehydration when about 10 per cent. of the total body water has been lost.

Output from the lungs.—The expired air is saturated with water vapour at 37° C. Under normal conditions only about 300 ml./day are lost in this way. When the inspired air is very dry, losses may be considerable. On the slopes of Everest, for instance, the cold dry air draws off much more moisture from the lungs than is lost in a temperate climate. The losses are increased by the increased ventilation of the lungs necessitated by the low oxygen content of the inspired air. It is believed that earlier Everest climbers became dehydrated from this cause which impaired their fitness for the final assault. In Sir John Hunt's successful expedition this point was appreciated and special attention was paid to the water intake of every member of the expedition. Each was made to drink 5 to 7 pints (3 to 4 *l.*) daily (Pugh & Ward, 1953). This apparently small point in physiology probably preserved the fitness of the climbers and may have made the difference between success and failure in the final assault on the summit.

Output from the gastrointestinal tract.—The small loss of water in the fæces is the balance of large exchanges which take place in the intestines. The saliva, the gastric secretions, the bile and the secretions of the pancreas and glands of the small intestine may together make up 8 *l.* or more fluid daily. All but a small proportion of this is normally reabsorbed in the gut. If, however, there is diarrhœa, vomiting or an intestinal fistula, fluid losses may be large and cause dehydration. In infants and small children particularly, gastrointestinal disturbances with diarrhœa and vomiting may cause a rapid and dangerous reduction in the total body water.

Output from the kidneys.—The volume of the urine is very variable and in general reflects the fluid intake. Yet there is a limit to the ability of the kidneys to concentrate the urine. The total osmolarity * of the urinary solutes on a normal diet is about 1200 mosM. daily. With a normal urine of specific gravity of about 1·020, this amount of solutes will be excreted in about 1500 ml. of urine. With maximum concentration by the kidneys, the urine specific gravity will be 1·040 and the volume about 900 ml./day. This is about the minimum volume of urine that a subject on a good diet must excrete (Weisberg, 1953) if he is to avoid retention of nitrogen and salts.

By reducing the intake of protein and salts in the diet, the load of urinary solutes may be reduced to 300 mosM. or less. In this way the daily excretion of urine can sometimes be reduced to 500 ml. or even less without the deleterious effects mentioned above. This is a practical point ; for a protein-free and salt-free emergency ration in lifeboats will help survivors of shipwrecks to conserve their body water by reducing the urinary loss to a minimum (Chapter 60).

The normal control of the urine volume depends on a regulatory mechanism, elucidated mainly by Verney (1957), which involves a nerve centre in the hypothalamus and a hormone secreted by the posterior pituitary gland regulating fluid absorption in the renal tubules. The centre in the hypothalamus contains cells—osmoreceptors—which are sensitive to changes in concentration of the solutes in the plasma. A dilution of the plasma (as after drinking a glass of water) stimulates the receptor cells which are connected by nerve fibres with the posterior pituitary gland. The secretion of the antidiuretic hormone by the gland is inhibited, and a diuresis sets in. Conversely, if the plasma becomes concentrated, the osmoreceptors are stimulated and signal the posterior pituitary to increase the secretion of the antidiuretic hormone and a diminished urine flow results. If the hypothalamus or posterior pituitary gland is injured by disease, secretion of the hormone may be impaired or stopped. Very large volumes of dilute urine are passed. This condition is known as diabetes insipidus.

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* One gram molecule of any un-ionised substance is equal to 1 osmol (osM.), and 1 milli-osmol (mosM.) is one-thousandth of an osM. For monovalent ions, 1 mEq. is equal to 1 mosM., but for divalent ions 1 mEq. is equal only to 0·5 mosM.

The Water Balance in Infancy

At birth the full function of the kidneys is not developed, and for the first 2 or 3 days of life the daily urinary volume is only about 20 ml. The volume of the colostrum may be little more than this. Kidney function improves simultaneously with the development of lactation. At 2 weeks the urinary volume is usually about 200 ml. and the volume of milk ingested about 500 ml. At 3 months the volume of milk may be 800 to 900 ml. and the urine volume about 300 ml. daily. The excess water is eliminated by evaporation, at a higher rate than is usual in adults. Naturally there are great variations. Infants are particularly liable to lose large quantities of fluid by diarrhœa and vomiting. Indeed dehydration is a common feature of many febrile illnesses in infancy and early childhood.

Water Retention and Depletion

Excess fluid in the body becomes apparent as *œdema*, which causes the subcutaneous tissues to pit when pressure is applied with the finger. But it is important to remember that this simple clinical test is not very sensitive ; œdema is not usually apparent until the body water is increased by 10 per cent. or more. Over-hydration sometimes results in œdema of the lungs.

Dehydration can be diagnosed without laboratory aids by the sunken features, particularly by the eyes which recede into the orbits. The skin becomes loose and lacks elasticity. On pinching it will stand up, away from the subcutaneous tissue.

SALT

Man's need for sodium chloride has been a subject of dispute since the beginnings of medical practice. The first known salt mines have been found in the Austrian Tyrol and date from the late Bronze Age, about 1000 B.C. In a scholarly review Kaunitz (1956) has pointed out that it is not accurately known when man first began to use salt. Sanskrit and its daughter languages have no common root for salt, so perhaps the Indo-Europeans at the time of their first migrations did not know of its use. However, salt was certainly available in the early civilisations and Homer called it ' divine.' For at least 3000 years sodium chloride has played " an amazingly important part in the lives of men. Wars have been fought over its sources, and for centuries its trade was more important than that of any other material" (Kaunitz). The salaries which we draw are in lineal descent from the salt money paid to the Roman soldiers. Imperial governments, such as those in the Roman provinces and in British India, have found a salt tax a convenient source of revenue; everyone paid it. Yet a separate supply of salt in addition to that present in the foods is not essential for man. There are good anthropological records of primitive people who do not use it.

Most people suffering from congestive cardiac failure and hypertension benefit if the salt in their diet is restricted. The hormones of the adrenal cortex—and in particular aldosterone—are now known to be responsible for conserving the body's salt and regulating the excretion of any excess. This is brought about by a direct effect on the renal tubules. It has been argued that the salting of food is a bad habit deleterious to health, in that it is liable to strain the regulating mechanisms of the adrenal cortex. However, Kaunitz suggests that the almost universal human demand for salt may be due to a stimulating effect, perhaps in the emotional sphere. This may be so and, if correct, table salt might well be classified with tobacco, wines, spirits, opium, cocoa, tea and coffee. All history goes to show that a judicious use of one or more of these comforts has always been associated with the higher achievements of the human race.

From those considerations it must be clear that to make recommendations for human needs for salt is very difficult. It is certainly true that the basic physiological processes of the body can go on without the deliberate addition of salt to food: yet for civilised man, salt appears to be an indispensable adjunct to life.

Sodium and Potassium Content of the Body

From the data given in Chapter 1 it can be calculated that in a normal man the extracellular fluids contain just under 2175 mEq. of Na and the intracellular fluids about 375 mEq. In addition there are some 900 mEq. present in the bones, making a total of about 3450 mEq. (200 g. of NaCl) in the whole body. Miller and Wilson (1953), using ^{24}Na, found values for the total exchangeable sodium in adult men and women varying from 1880 to 3140 mEq. By studying the exchange of ^{24}Na in samples of ribs obtained at thoracotomy operations, they conclude that only about 25 per cent. of the sodium in bone was exchangeable. Thus most of the sodium in the bones is held in a chemical form which is unavailable as an immediate reserve and cannot be measured by exchange methods, using isotopes.

By contrast, the potassium content of the extracellular fluids is only about 80 mEq., whereas the tissues contain about 3500 mEq. Four-fifths of this amount is in the skeletal muscles. The store of potassium in the bones is negligible.

TABLE 10, 2. *The daily sodium and potassium balance of a young man leading a sedentary life on a normal diet* (Passmore *et al.*, 1955)

(Mean of five daily measurements)

		Sodium mEq./day	Potassium mEq./day
Intake :	Food	135	60
	Condiments	0	0
		135	60
Output :	Urine	130	55
	Fæces	5	10
	Skin	negligible	negligible
	Total	135	65
Balance		0	– 5

NORMAL SODIUM AND POTASSIUM BALANCE

Table 10, 2 gives data obtained by us which show the sodium and potassium exchanges in a healthy young man. Intake is from the food and in the case of sodium from table salt. Output is in the urine and fæces ; occasionally significant amounts of sodium are lost in the sweat.

Intake of sodium and potassium

1. **Sodium.**—The dietary intake is very variable. Most normal people ingest 5 to 20 g. NaCl/day, corresponding to 70 to 350 mEq. Na. The food as served seldom contains more than 200 mEq. Na./day ; the remainder is taken as table salt.

Table 10, 3 gives the sodium content of a selection of foods. In general, foods contain relatively little sodium, but large amounts may be added in cooking. Also in most forms of processing and preserving, salt is added. Most bakers add salt to bread in a concentration of about 1 per cent. ; wheat flours contain less than one-hundredth of this amount in the natural state. Similarly butter, bacon and many other foods are commonly salted in preparation. Low salt diets must therefore be prepared mainly from unprocessed vegetable foods. Foods of animal origin usually contain more sodium.

2. **Potassium.**—The potassium content of foodstuffs is very variable ; natural diets provide from 50 to 150 mEq. K/day. The normal figure is about 65 mEq./day, equivalent to about 2 to 5 g. of potassium chloride. Disease processes attributable to potassium deficiency or excess never

TABLE 10, 3. *Sodium content of some common foods*

Food	Description	mEq./100 g.	g./100 g.
	Rich sources		
Bread	All extractions	17–29	0·39–0·67
Biscuits	Assorted	11–17	0·25–0·39
Cornflakes	...	29–44	0·67–1·01
Vegetables	Tinned	10–26	0·23–0·60
Beef	Corned	57–74	1·31–1·70
Ham	Boiled, lean	87	2·0
Bacon	Raw	33–52	0·76–1·20
Sausage	Raw	32–57	0·74–1·31
Shellfish	Fresh and tinned	3–13	0·07–0·30
Fish	Tinned and cured	17–44	0·39–1·01
Cheese	Cream	5–15	0·12–0·35
Cheese	Hard (Cheddar, etc.)	22–65	0·51–1·50
Butter	Fresh and salt	9–43	0·21–0·99
Margarine	...	14	0·32
Bovril	...	240	5·50
Marmite	...	150	3·45
Worcester sauce	...	61	1·40
	Moderate sources		
Cornflour	...	2·3	0·05
Oatmeal	Raw	1·5	0·03
Vegetables	Root and green, cooked and raw	0·1–6·0	0·01–0·14
Fruit	Dried, uncooked	1·4–3·4	0·03–0·08
Beef, pork, mutton	Raw	2·2–4·6	0·05–0·11
White fish	Raw	2·6–4·4	0·06–0·10
Egg	Fresh, whole	5·9	0·14
Milk	Fresh, whole	2·2	0·05
Cream	32 per cent. fat	1·5	0·04
Ice cream	...	2·3	0·05
Wines, ales and stout	...	0·1–1·7	0·01–0·04
	Poor sources		
Flour	Wheat, various	0·04–0·13	<0·01
Sago	Raw	0·15	<0·01
Rice	Raw	0·09–0·27	Up to 0·01
Shredded wheat	...	0·09–0·7	Up to 0·02
Sugar	...	Trace	Trace
Nuts	Various, without shell	0·04–0·22	Up to 0·01
Fruits	Fresh	0·04–0·22	Up to 0·01
Fruit juices	Fresh	0·02–0·20	Up to 0·01
Prunes	Dried	0·22–0·53	Up to 0·01
Lard	...	0·09	<0·01
Unsalted butter	...	0·22	<0·01

Note.—All the rich sources, except shellfish, have had sodium chloride added in the course of preparation.

arise primarily as a result of dietary deficiency or excess: nor is the treatment of such conditions confined to simple dietary corrections.

Table 10, 4 shows that most of the common foods contain moderate amounts. Cereals (including rice and wheat), cheese, eggs, fats and almost all fresh fruits contain less than 8 mEq. K/100 g. and have been used in constructing low potassium diets. There are certainly great variations

TABLE 10, 4. *Potassium content of some common foods*

Food	Description	Range (mEq./100 g.)
	Moderate sources	
Nuts	Assorted without shells	8–23
Fruit	Dried	15–26
Beef, mutton and poultry	Raw (edible portions)	7–10
Breakfast cereals	Various brands	4–14
Vegetables	Root and green, fresh	4–20
Vegetables	Root and green, tinned	3–10
Fish	Various types	3–10
Eggs	Fresh, whole	3·5
Milk	Fresh, whole	3·5
Cream	...	1–2
Cheese	Hard and soft	2–4
Bread	Various extractions	3–8
Rice	Raw, various millings	3–5
Fruit	Fresh, edible parts (very variable)	2–10
Fruit juices	Fresh, concentrated	2–5
Coffee	5 min. infusion	2·2
Chocolate	Milk	12·0
	Poor sources	
Corn starch	...	0·10
Honey	Without comb	0·26
Sugar	White	Up to 0·05
Marmalades and jams	...	0·20–2·0
Olive oil	...	Up to 0·03
Butter	Unsalted	Up to 0·38
Margarine	...	Up to 1·48
Beer	Mild	1·18
Tea	5 min. infusion	0·4

in the potassium content of different samples of the same food. The figures in the table are really only of illustrative value and in accurate metabolic balance studies it is essential to determine the potassium content of the diet by analysis of an aliquot sample.

Output of sodium and potassium

Output in the urine.—(1) **Sodium.**—Most of the daily output of sodium is in the urine which usually contains 100 to 150 mEq./24 hrs., and reflects the dietary intake. Concentrations range from 40 to 100 mEq./*l.* In most subjects studied a well-marked diurnal variation in sodium excretion has been found. The highest excretion is usually at about midday and the lowest at night. The kidney tubules are able to conserve sodium by reabsorbing most of the sodium reaching them in the glomerular filtrate. This regulatory mechanism is controlled by the adrenal cortical hormones. If the body sodium is depleted as by excessive sweating, reabsorption may be almost complete and sodium chloride can no longer be detected in the urine by the test of adding silver nitrate, which yields a white precipitate of silver chloride. This test is useful in clinical practice in the tropics as an indication of the extent of a primary salt deficiency arising as a result of excessive sweating. In temperate climates difficulties of interpretation, arising from other factors, make the test of little value.

The efficiency of the adrenal cortex-kidney tubule mechanism for conserving sodium is of great biological value. When the adrenal cortex is destroyed in Addison's disease this mechanism is upset and large amounts of sodium are lost in the urine. Many of the clinical features of Addison's disease—notably the muscular weakness and low blood-pressure—result from lack of sodium in the body and can be relieved by giving sufficient salt. Occasionally the kidneys, as a result of disease, are unable to conserve sodium so that large amounts are lost in the urine and the body becomes depleted.

Healthy kidneys have no difficulty in excreting any quantity of salt that may be taken in the diet, provided there is a sufficient excretion of water. As already stated, the kidneys cannot concentrate the urine above a specific gravity of 1·040. This limit to the kidneys' capacity to excrete salt is of practical importance for survival in deserts or after shipwreck, when fresh water may not be available.

Sodium accumulates in the body in congestive heart failure and in certain types of kidney disease. The use of low salt diets in the treatment of these diseases is discussed in Chapter 40. Excessive therapeutic doses of cortisone or other adrenal cortical hormones also inhibit sodium excretion and lead to sodium excess in the tissues.

2. **Potassium.**—The output of potassium in the urine reflects closely the dietary intake. In healthy people on a normal diet it is around 60 mEq./24 hrs. Increased amounts of potassium are found in the urine whenever the tissues are losing potassium. Perhaps the most important cause is a breakdown of cellular proteins such as occurs in diabetes, underfeeding and after injury. In most tissues 1 g. of nitrogen is associated with about 2·7 mEq. of potassium. By means of metabolic studies it is possible to determine from the nitrogen and potassium balance the K/N ratio of the cellular material lost or gained ; this may be a useful guide to changes in the cells. Some potassium can be displaced from the cells by an excess of other cations, especially Na and H. Any condition giving rise to acidosis is liable to cause potassium loss, as also is a sodium overload, such as may arise from excessive intravenous saline therapy.

The adrenal cortical hormones, especially aldosterone, cause increased potassium excretion in the urine. Excessive production of aldosterone by the adrenal cortex causes large losses of potassium in the urine and consequent deficiency in the cells and a low level in the blood. This effect is not confined to one adrenal hormone, as large urinary losses of potassium may arise in patients with adrenal tumours (Cushing's syndrome) and also after overdosage with cortisone and other adrenal hormones. In adrenal insufficiency (Addison's disease) there may be impaired potassium excretion and raised levels in the blood. In certain types of renal disease the kidney is unable to retain potassium and much may be lost in the urine, with consequent potassium depletion.

Output in the gastrointestinal tract.—In health the fæces contain very small amounts of sodium (about 5 mEq./day) and only a little more potassium. The digestive juices contain large amounts of both, but these are normally reabsorbed in the gut. However, diarrhœa may cause large losses in the stools ; in this way the body may be depleted in amounts up to 90 mEq./24 hrs. of both sodium and potassium (Darrow & Pratt, 1950). It has long been known that sodium depletion is an important complication of cholera, arising as a result of the losses in the numerous stools, and more recently it has been realised that potassium depletion may also occur. Thus Hansen (1956) showed that when severe diarrhœa was present in infants suffering from protein malnutrition (kwashiorkor) a state of potassium deficiency frequently developed ; as much as 10 to 30 per cent. of the total body potassium may be lost, and this may be responsible for sudden cardiac failure. Similar losses can also occur in adults with diarrhœa, either acute or chronic, and from intestinal fistula.

Output through the skin.—Unless there is active sweating, the loss of sodium through the skin is small and usually neglected in balance studies. When there is active sweating the situation is very different. The sodium content of sweat varies greatly from one individual to another, but generally lies within the range 20 to 80 mEq./*l.* People acclimatised to heat usually conserve some of their body sodium by secreting a dilute sweat containing only about 30 mEq./*l.* As the daily volume of sweat may be several litres (8 *l.* is the measured record) it will be appreciated that sodium losses from this source may be very large and much greater than the urinary loss. In such circumstances, unless there is a corresponding increase in salt intake, salt depletion will quickly follow.

Sweat contains about 9 mEq./*l.* of potassium, range 5 to 16 (Ahlman *et al.*, 1952) and losses from the skin are usually negligible.

THE EFFECTS OF SODIUM DEPLETION

Sodium depletion is characteristically associated with dehydration, as for instance in heat exhaustion. The essential chemical pathology is a reduction in the extracellular fluid. The blood volume is also reduced and the red corpuscles form a higher proportion of the blood volume as shown by a high hæmatocrit value. As a result of the low blood volume, the veins are collapsed, blood-pressure is low and the pulse is rapid. Sodium chloride usually cannot be detected in the urine. Thirst is often absent, although the mouth is dry. The characteristic symptom is muscular cramp, which is well known to miners who work in hot pits. Cramps also occur in cholera and in Addison's disease associated with sodium depletion. Mental apathy is usually well marked. Loss of appetite and vomiting may also be present. A full account of the symptoms and signs of salt deficiency is given by McCance (1936), based on observations made on himself and his pupils after experimental depletion. A guide to the extent of the deficiency of both sodium and water is provided by the level of serum sodium and the hæmatocrit reading (normal values, 140 mEq. Na/*l*. and 40 per cent. respectively). Although sodium and water deficiency can usually be detected easily enough from the history and clinical examination, the extent of the deficiency cannot be so easily judged. It is now well recognised that sodium depletion may be present without water depletion—a condition which has been called *water intoxication*. This is fully described and discussed by Black (1957). The condition occurs when thirst provoked by heavy sweating is quenched by water to which no salt has been added. It may also arise in the treatment of water or sodium deficiency if too much water is given either intravenously or by mouth. In addition to anorexia, weakness and mental apathy, there may be muscular twitchings, convulsions and even coma which may be difficult to distinguish from uræmia.

The Effects of Sodium Excess

Any excess of sodium in the body accumulates principally in the extracellular fluids. The increased concentration of sodium is partially offset by an increase in these fluids. Sodium excess may therefore result in œdema.

Rats fed on diets containing a large excess of salt develop enlarged hearts with high blood pressure and abnormal electrocardiograms. In some the kidneys are also enlarged and glomerular nephritis may occur. Experimental chronic salt toxicity has been fully described by Youmans (1957), but he is properly very cautious in applying these results to man.

The Effects of Potassium Deficiency

The chief features of potassium deficiency are muscular weakness and mental apathy. The weakness is well illustrated by a rare disease, *familial periodic paralysis*. The patient is subject to recurrent attacks of muscular weakness and paralysis which may last for 24 hours or more. The attacks are associated with low levels of serum potassium. They are probably caused by a periodic over-secretion of aldosterone by the adrenal cortex.

The absence of characteristic symptoms may account for the failure to recognise the importance of potassium deficiency in the past. Only recently has its importance in conditions such as diabetic coma and kwashiorkor been realised. Most of the potassium is in the cells and, as no direct way exists for estimating the chemical content of the cells, biochemical diagnosis is difficult. The level of potassium in the plasma may bear little relation to the amount in the tissues. When tissues are breaking down and losing potassium, plasma levels may actually be higher than normal.

The cardiac muscle is involved in the general muscular weakness with sudden death as a possible consequence. Electrocardiographic changes are often of diagnostic value. A prolonged QT interval and a broad low T-wave are commonly found.

The Effects of Potassium Excess

The toxic effects of potassium fall first on skeletal and cardiac muscle and so broadly resemble the effects of depletion. Muscular weakness and mental apathy are generally marked. High levels of potassium in the blood are found only in association with other severe diseases such as renal failure, adrenal insufficiency or shock after injury, in which condition the potassium can leak out into the blood from the damaged cells. An excessive dose of potassium given by vein may cause death by stopping the heart.

CHLORIDE

As stated in Chapter 1, chloride is very closely associated with sodium in the extracellular fluids. The normal chloride content of the blood is 98 to 106 mEq./*l*. Chloride is taken into the body largely as sodium chloride and the excretion of Cl in the urine, sweat and gastrointestinal tract usually follows closely the excretion of Na. However, Cl may be lost to the body in urine in association with NH_4, or in vomit in association with H. This leads to the subject of acid-base equilibrium.

ACID-BASE EQUILIBRIUM

Human life is possible only if the blood is kept within a narrow range of alkalinity. In health the blood is maintained very accurately at *p*H 7·4 (*p*H is the negative logarithm of the hydrogen-ion concentration). This precise equilibrium is maintained by two mechanisms. First, the rate of excretion of carbonic acid (a weak acid) through the lungs acts as a very fine adjustment. Secondly, the kidney is able to excrete urine with either an acid or an alkaline reaction. In disease of the lungs or of the kidneys, these controlling mechanisms may no longer work normally and an acidosis or alkalosis results. Such effects are of great interest to the physiologist and of much practical importance to the physician, but are outside the scope of this book. Here we shall be concerned only with the dietary aspect of acid-base equilibrium which, compared with the renal and respiratory aspects, is very minor.

It has long been known that the urine of the rabbit is normally alkaline and the urine of the dog acid. This is related to the nature of their diets. The urine of an omnivorous animal such as man may be either acid or alkaline. It is usually slightly acid, but in vegetarians it is often alkaline, and in large meat-eaters more strongly acid. This is because, in fruits and vegetables, the cations Na and K are associated with weak organic acids, so that these foods yield an alkaline ash. In all flesh foods there is a slight excess of the anions PO_4 and SO_4 and these foods yield an acid ash. The differences are of no importance in practical dietetics since the healthy kidney can easily make the necessary adjustments by excreting a correspondingly alkaline or acid urine.

An anomaly, however, exists, for although fruits and vegetables are—from the physiological point of view—alkali-producing foods, in fact they may taste acidic and are often thought to be ' acid ' foods. Many food faddists and some physicians (who should know better) have made much of the ' acidity ' of fruits and vegetables. This acidity is due to the presence in plant tissues of a variety of organic acids—citric acid (citrus fruits, pineapple, tomato and most summer fruits), malic acid (apples, plums and tomatoes), benzoic acid (cranberry and blaeberry), tartaric acid (grapes), oxalic acid (strawberries, unripe tomatoes, rhubarb and spinach). Mottram and Graham (1956) give some details of the amount of acids present in fruits and vegetables. They state that very few foods are ever as acid as gastric juice. Further, the body can easily oxidise malic and citric acid. Benzoic acid is excreted by the kidney as hippuric acid. Tartaric acid is hardly absorbed at all. Oxalic acid forms insoluble calcium salts and so is not easily absorbed from the intestines ; nevertheless it can also be oxidised and excreted. Figures given by Mottram and Graham indicate that the intake of these acids, even from large quantities of fruits and vegetables, is well within the capacity of the body to deal with them. They do not cause acidosis. The digestive disturbances from which young gentlemen are known to suffer after an illicit visit to an orchard are attributable to the sudden intake of large quantities of indigestible cellulose.

However, there are two organic acids produced within the body which can give rise to acidosis. These are lactic and acetoacetic acid. Large quantities of lactic acid may accumulate in the blood after severe muscular exercise (up to 100 mg./100 ml.). The rapid breathing during recovery from exercise helps to restore the acid-base balance by blowing off carbonic acid.

Acetoacetic acid (and its derivative β-hydroxybutyric acid) are produced in excess in untreated diabetes and in other conditions with an unbalanced and predominantly fat metabolism (Chapter 6). These acids accumulate in the blood and as both are stronger acids than carbonic acid, they displace the bicarbonate in the blood. As a result there may be a serious fall in the alkalinity of the blood and the dangerous condition of acidosis develops.

CHAPTER 11

MINERALS (1)

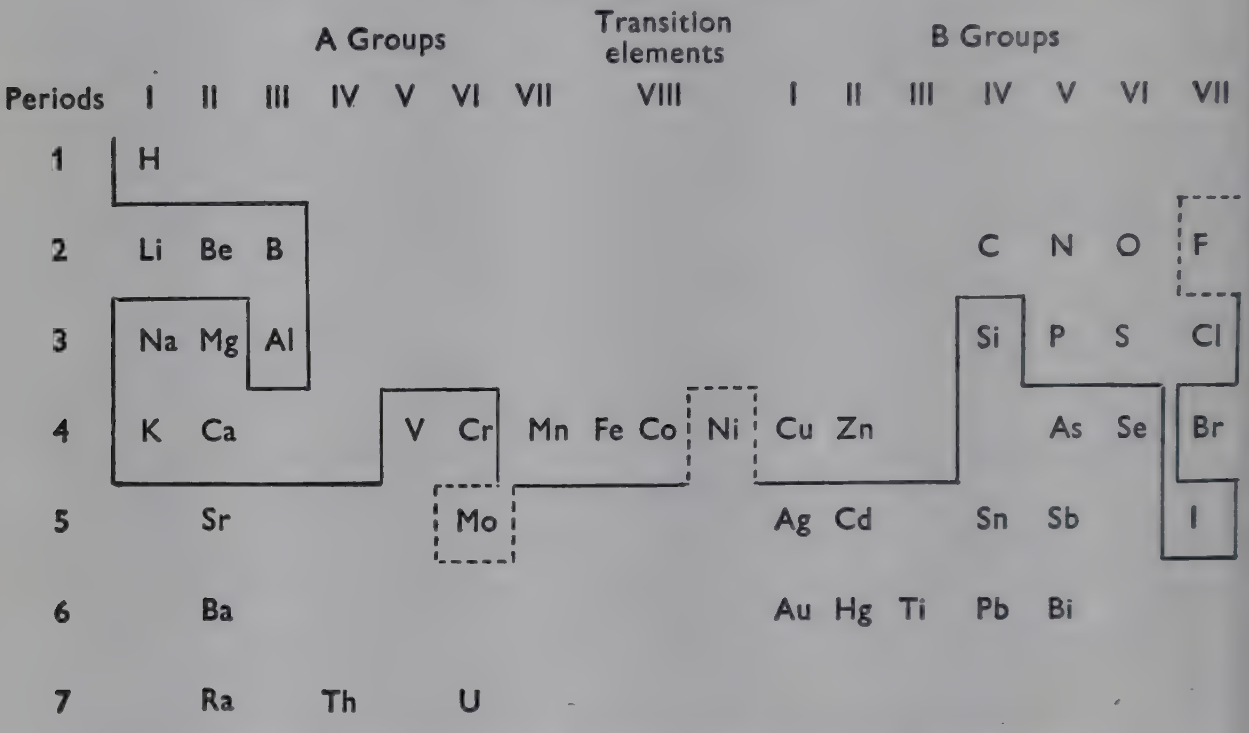
AT one time learned men were inclined to interpret literally the biblical story that " the Lord God formed man out of the dust of the ground." Not least of the intellectual revolutions that stemmed from Darwin's Theory of Evolution was the alternative belief that man originated out of the sea. Modern knowledge supports this latter view, since it is now known that the mineral composition of man's body is strikingly different from that of the land on which he walks. The surface of the earth is chiefly composed of oxides of silicon and aluminium. Neither of these two elements occurs to any important extent in the human body nor, so far as is known, do they contribute to its metabolic processes. The explanation is simple ; the oxides of both elements are virtually insoluble in water ; so much so that although seashores are strewn with silica sand and sometimes alumina clay, neither silicon nor aluminium contributes to the salinity of the sea.

The theory that man is descended from some remote marine ancestor is consistent with the fact that his extracellular fluid has definite similarities in mineral composition to that of the sea as it was likely to have been many millions of years ago (MacCallum, 1926 ; Pantin, 1931). Sea water contains measurable quantities of the following elements (arranged in order of their concentration) : chlorine, sodium, magnesium, calcium, sulphur, nitrogen, potassium, bromine, carbon, iodine, iron. It also contains traces of phosphorus, although the greater part of this element is immediately taken up by plankton, the floating organisms of the sea, and incorporated into their organic structure. All of these elements contribute to the nutrition of the human body, with the apparent exception of bromine. It is possible, of course, that bromine is a comparatively new component of the sea, which is gradually increasing in salinity by the constant addition of soluble salts washed down by the rivers, and by simultaneous evaporation of water from its surface.

The survival of man on the earth has clearly depended on an ability to obtain by selection the various chemical elements necessary for life, by choosing for his food those plants and animals that provide them. For instance, the need for phosphorus could never have been satisfied by the waters of the sea even in the most remote times of evolutionary history, and must have depended from the beginning on plant life which alone is able to extract this element from water and soil. The amount of phosphate in the earth's crust is so small that without plant life animal life would have been impossible. Yet plants are such a good source of this element that phosphorus deficiency raises no practical problem in human nutrition.

From the Periodic Table as illustrated below, it will be seen that the elements known to contribute to the organisation of the human body are chiefly those with relatively low atomic weights in the upper part of the table. This selection seems to be based on the two factors of solubility and general distribution in foodstuffs. Thus aluminium and silicon are excluded because their naturally-occurring compounds are almost insoluble, whilst lithium is so thinly and variably distributed in the earth's crust that the human body appears to have evolved without depending on it.

TABLE 11, 1. *The Periodic Table simplified to show the elements of chief importance in human nutrition and toxicology. Those above the line are known to be essential components of the human body and thus essential nutrients*



	A Groups							Transition elements	B Groups						
Periods	I	II	III	IV	V	VI	VII	VIII	I	II	III	IV	V	VI	VII
1	H														
2	Li	Be	B									C	N	O	F
3	Na	Mg	Al									Si	P	S	Cl
4	K	Ca			V	Cr	Mn	Fe Co Ni	Cu	Zn			As	Se	Br
5		Sr				Mo			Ag	Cd		Sn	Sb		I
6		Ba							Au	Hg	Ti	Pb	Bi		
7		Ra		Th		U									

Dotted lines indicate those of questionable nutritional significance.

The successful building of a human body depends fundamentally on two factors : (1) man's ability to find the right foods—plant or animal—that contain the necessary chemical elements, and (2) the ability of his body to accept or reject the elements that the food provides. As regards the latter, the various elements necessary for human health can be classified as follows.

1. Absorbed and easily excreted.—Food after digestion is chiefly absorbed in the form of relatively simple, soluble compounds or ions. Most simple compounds of hydrogen, oxygen, carbon, nitrogen, sodium, potassium and chlorine are easily absorbed and, once absorbed, these elements are freely excreted in the urine, or in the breath in the case of carbon dioxide.

Calcium, magnesium and phosphorus are partly combined in complex insoluble or indigestible compounds which are imperfectly absorbed so that a chemical analysis of the amount of each present in a diet does not necessarily reflect its nutritive value in respect of them. Nevertheless, once absorbed, they are freely excreted. In general, the gut absorbs monovalent ions such as Na and Cl more readily than divalent ions such as Ca and SO_4. For instance NaCl is more readily absorbed than $MgCl_2$, even though the latter is more soluble in water.

The elements listed above have formed the basis of living matter since its earliest origins in the sea. It is therefore not surprising that the human kidney is able to eliminate them. Provided that the kidneys are working normally, they produce no harmful effects if they are present in excessive amounts in natural foods. Only artificial preparations of these elements, such as yellow phosphorus, may be poisonous.

2. **Poorly absorbed and poorly excreted.**—In contrast to the elements so far mentioned, which provide the bulk of man's daily food, the essential metals—manganese, iron, cobalt, copper and zinc—normally occur only in traces in food. The human kidney is less well adapted to eliminate any excess that may be consumed, probably because they are largely bound to proteins. The kidney appears to be incapable of excreting iron. The chief defence against an excessive accumulation of iron in the body is provided by the intestinal tract which normally refuses to absorb more than the body requires. An alternative route of excretion is provided for manganese which is eliminated in the bile, whilst zinc is excreted in the pancreatic juice. Small but excessive amounts of copper and cobalt, taken over a long period, are gradually eliminated in the urine. But a single large dose of copper salts is immediately rejected in a dramatic way since they are powerful emetics. Zinc salts taken by mouth also cause vomiting, as do those of antimony.

Other elements

Some mention should be made of the elements listed below the line in Table 11, 1. Molybdenum, nickel and fluorine have not yet been proved to be essential nutrients for man ; yet there is enough circumstantial evidence in their favour to warrant some further mention of them later in Chapter 12. The remaining elements are not, so far as is known, essential for life ; they may sometimes contaminate food and so are important in connection with food poisoning. Some are deliberately introduced into the human body for therapeutic and diagnostic purposes.

Lithium.—The reason why this alkali metal does not contribute to the economy of the human body is probably the very simple one that its distribution in the earth's crust is extremely sparse. Small amounts are not poisonous since the kidney excretes it in the same way as sodium.

Beryllium.—This light metal is extremely poisonous, in contrast to the next in the series of alkali earth metals—magnesium and calcium. The probable reason is that beryllium phosphate is completely insoluble, so that reactions dependent on ionised phosphate are inhibited by the metal. It is used in several industries : electric, steel, synthetic jewellery and atomic piles. Beryllium dust irritates the lungs and skin of those exposed to it and would be poisonous in food.

Boron.—This is another element against which the body appears to have no defences. Boric acid has enjoyed an unfortunate vogue as a disinfectant in lotions, ointments, surgical dressings and baby powders. It does not destroy the *Staphylococcus aureus* and is therefore of small antiseptic value; yet if absorbed from a large open wound it can cause vomiting, diarrhœa and even fatal collapse.

Aluminium and silicon.—These elements, as already mentioned, are too insoluble in their natural forms to be absorbed by the body. Their very insolubility gives them a use in medicine; aluminium silicate (kaolin) is widely used as an absorbent in the treatment of diarrhœa, whilst magnesium trisilicate is useful for neutralising excessive acid in the stomach. At one time it was thought that aluminium cooking vessels might be a cause of chronic poisoning, but aluminium is too insoluble for this to occur.

Vanadium.—It is curious that this element does not seem to be necessary for man although it is widely distributed on the earth's surface. Small amounts are frequently present in clays, rocks, coal and natural oil. Traces are commonly present in plants. The only animal, so far as is known, that uses vanadium is the sea-squirt (*Ascidium*). Compounds of vanadium, which are mostly coloured, are used in industry for the making of ink, dyes, paints, glass, insecticides and photographic materials.

Chromium.—The naturally occurring compounds of chromium are sporadically distributed on the earth and very insoluble. It is understandable, therefore, how this metal has no place in life. Artificial soluble salts of chromium injected into the body damage the renal tubules.

Arsenic.—This widespread metal has a great reputation as a poison. It combines with sulphydryl (SH) groups in the body and thus inactivates many enzymes. Traces of arsenic are commonly found in human tissues, but there is no certain evidence that it is a necessary nutrient.

Selenium is about as poisonous as arsenic. It is present in some soils and is taken up by plants. Animals that graze on them become poisoned with 'alkali disease.' Selenium is so like sulphur in chemical properties that its poisonous action has been attributed to its capacity to replace sulphur in essential enzyme systems.

Bromine.—It is surprising that the human body has no apparent use for bromine in view of its occurrence in the sea and in marine plants and animals. The Tyrian purple of classical times was a di-bromo-indigo extracted from shellfish. The human kidney and the body generally seem to handle bromides in much the same way as chlorides. Bromides have been used to depress the higher centres of the brain when given over long periods, as, for instance, in epilepsy. Chronic poisoning (brominism) results if more than 15 per cent. of the chloride in the blood is replaced by bromide.

It is a curious anomaly that the human body requires iodine which is by far the heaviest element (atomic weight, 127) known to be a necessary nutrient, and yet can dispense with bromine—another halogen that is readily absorbed and is not only lighter but exists in greater concentration in present-day sea water.

The remaining elements listed in Table 11, 1 are:

Period 5.—Strontium, silver, cadmium, tin and antimony. The scallop is the only known animal to use cadmium, probably in much the same way as the human body uses zinc. The metabolism of strontium is discussed on page 170.

Period 6.—Barium, gold, mercury, titanium, lead and bismuth.

Period 7.—Radium, thorium and uranium.

All of these are of medical interest, either because they are used fo therapeutic and diagnostic purposes or because they are sometimes a cause o poisoning, probably because their excretion from the body is variable and generally inefficient. Their high atomic weights make it most unlikely that any of them are essential nutrients: many are protein precipitants. It should be noted, however, that some form salts that are insoluble in water and are thus non-poisonous; tons of barium sulphate are swallowed every year by patients undergoing radiological examination of the intestinal tract: no harmful effects result because this salt is totally insoluble in water. Yet soluble salts of barium are highly poisonous.

Elements Essential for Man

Man's supply of hydrogen, carbon, nitrogen and oxygen is derived from the carbohydrates, proteins and fats of his diet and (in the case of hydrogen and oxygen) from water. The supply of sodium, potassium and chlorine has been discussed in Chapter 10. The remaining essential elements are considered in the following pages.

CALCIUM

The body of an adult normally contains about 1500 g. of calcium. At least 99 per cent. of this amount is present in the skeleton, where calcium salts (chiefly phosphate) held in a cellular matrix provide the hard structure of the bones and teeth. Obviously all of this calcium comes from the diet. Among common foods, the calcium-containing protein of milk (caseinogen) is much the richest source, which is one reason why milk and cheese are especially valuable for growing children. Half a litre (just under a pint) of cow's milk contains about 0·6 g. of calcium. Most other foods contribute much smaller amounts. The calcium retained in the normal human skeleton has therefore been extracted from a very large volume of food, even when the diet has contained abundant milk and cheese.

Physiology

Nearly 200 years ago John Hunter showed that the architecture of the bones is completely reorganised during the process of growth; no single strut or brace of bone remains fixed and permanent in any part of the body. Two different kinds of cells are constantly altering the structure of the bones, even in adult life. While the osteoblasts lay down fresh calcium salts, especially where new stresses have developed, osteoclasts are constantly eroding redundant calcium deposits. A well-adjusted equilibrium exists between the calcium coming and going from the bones and the calcium present in small but normally constant amounts in the fluids of the body. Thus the bones not only provide physical support to the body but also a large reserve of two essential elements—calcium and phosphorus—on which the body can draw in case of need.

Calcium outwith the skeleton.—The amount of calcium in the extracellular fluids and soft tissues of a normal adult does not exceed 10 g. Much of this is bound to protein, as it is in milk. The various ways by which calcium contributes to the vital processes of living cells are still not clearly defined, though its intimate association with proteins is shown by the fact that the fibrinogen of blood and the proteins of damaged tissues will not clot in its absence. Similarly the enzyme rennin is dependent on calcium for its activity. This enzyme is secreted by the stomach of young mammals and causes the curdling of milk (*i.e.* clotting of caseinogen) as a preliminary to digestion.

The physiological activity of calcium can be suppressed by the artificial addition of citrates or oxalates. Sodium citrate once enjoyed a great vogue as an additive to cow's milk for infant and invalid feeding and is still sometimes used for this purpose in the belief that by thus inhibiting the normal curdling of caseinogen in the stomach, the milk will be rendered more digestible.

Calcium in the blood.—The amount of calcium in the serum is about 10 mg./100 ml. (normal limits, 9 to 11 mg.). None is present in the red blood corpuscles. About half this amount is bound to the serum albumin and half is in ionised solution. If the level of albumin in the serum is lower than normal in consequence of protein deficiency, there is a corresponding reduction in the level of protein-bound calcium. This produces no obvious metabolic disturbance, in marked contrast to the effects of a reduction in the ionised portion of serum calcium as sometimes happens, *e.g.* in rickets. If the blood becomes alkaline (as after excessive vomiting with loss of chloride anions) there may be relative excess of sodium cations ; consequently the ionisation of calcium is depressed although the total amount of calcium in the serum remains unchanged.

Effects of reduction in circulating ionised calcium.—The motor nerves become over-susceptible to stimuli. This particularly affects the face, hands and feet, producing the clinical features of *tetany.* Muscles lose tone and become flaccid, so that infants with rickets are late in sitting, standing and walking. The isolated animal heart ceases to beat when transfused with fluid lacking calcium ; however, there is no good evidence that calcium deficiency in the myocardium is ever a cause of heart failure in man.

The amount of calcium in the body is the balance of intake (first from the mother and later from foodstuffs) against the output excreted in the urine and fæces. Any attempt to estimate the true dietary requirements for calcium must take into account both intake and output.

INTAKE

Before birth and during lactation.—For the fœtus the supply is assured, since the mother's body will always yield all the calcium that the prospective infant requires. If she is short of calcium herself she may develop osteomalacia in consequence (Chapter 30). In this sense, the fœtus is a true parasite. After birth the infant becomes dependent for the first time on a dietary source to supply the calcium necessary for the development of his bones. The natural source is his mother's milk, which provides about 30 mg. Ca/100 ml., no matter how malnourished she may be. Malnutrition is more important in influencing the *volume* of milk that the mother can yield, though this varies very much, even in apparent health. Test-weighings of infants before and after breast-feeds show that a good mother produces on average 500 ml. milk/day after a few weeks and at 6 months 1 *l.* or more, providing at least 300 mg./day of calcium. If the mother's milk fails, the infant is often fed on cow's milk which not surprisingly contains about four times more calcium (roughly 120 mg./100 ml.), since a calf calcifies its skeleton much faster than a human infant. There is no good evidence as yet that infants fed cow's milk, and therefore having a higher calcium intake than breast-fed infants, suffer any disability from the excess.

In childhood and later life the supply of calcium is less certain. Table 11, 2 shows the calcium content of some common foods ; from this it will be seen that milk and cheese are the most valuable sources. However, pulses, other vegetables and particularly cereal grains often contribute the greatest part of the daily calcium intake. Cereals—although their calcium content expressed as mg./100 g. is not impressive—are frequently the chief contributors because of the large amounts eaten. By contrast, there are certain foods that are extraordinarily rich in calcium, yet which are eaten so rarely or in such small amounts that they contribute little to the regular intake.

Drinking water can provide significant amounts. In Great Britain the average intake from this source is about 75 mg. Ca/day ; but the variations are large : from 0 in water from peaty, acidic hill lochs in Scotland to 200 mg. or even more in water obtained from wells sunk in chalk or limestone.

Absorption

The calcium content of a diet, calculated from such figures as those given in Table 11, 2, is no direct index of the amount actually utilised by the consumer since the absorption of calcium in the gut is always far from complete. Normally between 70 and 80 per cent. of the calcium in the diet is excreted in the fæces. The many factors that influence the extent of calcium absorption are still not fully understood, though some at least are known, as described in the following paragraphs. The subject has been reviewed by Nicolaysen and his colleagues (1953) and by Malm (1958).

Substances assisting absorption

Vitamin D.—This vitamin, derived either from the food or from the skin exposed to ultraviolet light, assists the absorption of calcium from the gut. Vitamin D can also influence the normal relationships that exist between the amount of calcium absorbed from the gut, present in the blood and bones, and excreted in the urine.

Proteins.—The absorption of calcium in the small intestine is certainly

TABLE 11, 2. *Calcium content of some common foods*

(Selected values from various food tables)

Food	Description	Range (mg./100 g. or 100 ml.)
Cheese	Hard—from whole or skimmed milk	500–1200
Cheese	Soft—from whole or skimmed milk, and processed	80–725
Milk	Cow's—fresh whole	120
Milk	Human	20–40
Nuts	Various—without shells	13–250
Pulses	Raw—dried	40–200
Herring	Raw—edible parts	70–100
Roots, gourds and stems	Raw—various, except potato	20–100
Vegetables *	Raw—green, leafy	25–250
Eggs	Fresh, whole	50–60
Oatmeal	Raw, 65 per cent. extraction	55–60
Whole wheat	100 per cent. extraction	30–40
Wheat flour	70 per cent. extraction	13–20
Millets	Most varieties	20–50
Fruits	Various—raw, fresh	3–60
White fish †	Fresh	17–32
Beef, mutton, pork and poultry	Raw—edible portions	3–24
Maize	Various millings	5–18
Rice	Raw, polished	4–10
Potatoes	Raw—all seasons	7–10

* Green vegetables most commonly used in temperate climates all fall in the lower part of the range and therefore contribute little to the calcium content of the diet.

† Sardines and other small fish eaten whole provide anything up to 400 mg. Ca/100 g. and may therefore be important sources of calcium.

influenced by the nature of other nutrients undergoing absorption at the same time. McCance and his colleagues (1942) first demonstrated the importance of proteins in facilitating calcium absorption. The probable explanation is that amino acids liberated in the course of protein digestion form very soluble calcium salts which are easily absorbed.

Substances interfering with absorption

Phytic acid.—In the 1920's Sir Edward Mellanby (1921 and 1925) demonstrated that puppies easily developed rickets when brought up on a diet poor in vitamin D and calcium, and containing large amounts of bread. The puppies that ate the most bread grew fastest and developed the most severe rickets. Mellanby was at first inclined to attribute this effect to the growth-promoting properties of the bread, which allowed the puppies to grow at a rate faster than their bones could lay down calcium. He soon found, however, that the effect was not due solely to the quantity of bread eaten ; there were also qualitative differences. Whole wheat flour was more rachitogenic than white flour, and oatmeal worse than either. This led him to postulate the existence of an anticalcifying factor in cereals. The gradual elucidation of the nature of this factor presents a fascinating chapter in the history of laboratory research. The story has been well told by Mellanby himself (1950). In brief, it was eventually proved that the anticalcifying factor is inositol combined with six phosphoric acid molecules to form the compound now known as phytic acid.

McCance and Widdowson (1942) published the first human experiments on the dietary influence of phytic acid. By feeding volunteers on breads of varying composition and comparing the calcium content of the diet with the amount excreted in the urine and fæces, they arrived at the following conclusions :

1. Calcium is much less freely absorbed from diets consisting largely of brown bread than from those consisting largely of white.
2. The amount of calcium absorbed from diets containing brown bread could be raised by adding calcium to the bread.
3. The absorption of calcium from white bread could be prevented by adding sodium phytate.
4. The absorption of calcium from brown bread diets could be improved by removing phytic acid from the bread. The latter point is illustrated in Table 11, 3, taken from their data.

TABLE 11, 3. *Intake and absorption of calcium on diets largely composed of bread*

Bread	Subject 1			Subject 2		
	Intake	Absorption		Intake	Absorption	
	mg./day	mg./day	Per cent. of intake	mg./day	mg./day	Per cent. of intake
Brown	550	89	16	522	57	11
Dephytinised brown	590	231	39	566	169	30
White	488	250	51	478	219	46

These experimental results became available at a crucial time in British history when the final outcome of the Battle of the Atlantic still lay in the balance. Food from North America was vital, but there was a shortage of shipping to bring it ; consequently a change from white bread to bread containing more of the whole grain became essential, as further described in Chapter 17. The proper and logical advice given by the Medical Research Council to the British Government was that calcium carbonate should be added to the new ' National Loaf ' in amounts sufficient to offset its increased content of phytic acid. This was accordingly done.

Since that time of crisis there have been some second thoughts. In the first place it is realised that many cereals contain an enzyme—phytase—capable of splitting off the phosphate from the inositol, leaving both the phosphate and any calcium attached to it available for absorption. Rye in particular and also wheat contain enough phytase to lead to considerable destruction of phytic acid during the process of leavening bread ; during this process conditions for enzymic action are good. Thus although 50 per cent. or more of the phosphorus in the original whole grain may be in the form of phytic acid, the amount in the final product—bread—may be very much less. However, oats contain little phytase and what there is may be destroyed by commercial kiln heating. This perhaps accounts for their especial tendency to produce rickets in puppies, as originally found by Mellanby. On the basis of his animal experiments it might be expected that rickets would be especially common among porridge-eating Highlanders in Scotland. In fact the disease was never prevalent in Scotland except in the cities. Mellanby himself suggested that the amount of milk taken with porridge might provide enough calcium to offset the rachitogenic properties of oatmeal, but perhaps there is a better explanation. Cruickshank and his colleagues (1945) struck a blow in defence of the honour of Scotland's traditional cereal when they showed that in four Aberdonian volunteers the phytate phosphorus present in oatmeal was largely liberated in the digestive tract and so caused little interference with the absorption of calcium. Perhaps the important point is that in those who eat oatmeal regularly the digestive juices may acquire the ability to split calcium phytate. For puppies on the other hand, oatmeal is an unfamiliar food.

This leads to the important question of adaptation to diets high in cereals and phytic acid and poor in calcium. There can be no question that many people throughout the world succeed in calcifying their teeth and bones whilst subsisting for long periods on diets of this kind. Walker (1951), in a scholarly review of the subject, concluded that " the importance of phytic acid as an anticalcifying factor in human nutrition has not been established." His chief argument against the interpretation of the experiments of McCance and Widdowson is that they were not continued long enough for the subjects to become adapted to the change in diet (p. 164).

In view of this conflict of opinion, what is the right advice about the need for adding calcium carbonate to wheaten bread and other cereals rich in phytic acid ? Probably the correct answer is that for people used to such cereals from childhood, it is unnecessary. But in Western civilisation, among people accustomed to white bread and a high calcium intake provided by dairy produce, any sudden alteration of dietary habits, such as a change to wholemeal flour, might cause considerable calcium depletion in the body. There is therefore still a case for continuing the addition of calcium carbonate to bread in Great Britain as an insurance, both for the individual and the community, against unexpected changes in customary eating habits.

Other factors which may interfere with calcium absorption

Phytic acid has been discussed at length because it is a difficult and controversial subject with important practical applications (Chapter 17). But there are further factors to be considered.

Phosphate.—Before the discovery of phytic acid it was generally believed that the *total* phosphate intake had a crucial influence on calcium absorption. This belief originated from animal experiments which were interpreted as showing that an excessive phosphate intake depressed the absorption of calcium, particularly if the supply of vitamin D was deficient. Many publications supported the idea that the calcium/phosphate ratio in the diet was all-important. Dietitians spent much fruitless time in attempting to calculate (from inaccurate food tables) the Ca/P ratios in diets prescribed by physicians possessing a too ready faith in the application to man of results obtained on laboratory animals.

Subsequent experiments on human subjects have shown that the total phosphate intake has little or no influence on calcium absorption, at least within the range within which these two elements normally occur in foodstuffs, and probably further. Malm (1953) for instance, has shown that six Norwegian men given excess phosphate by mouth in amounts sufficient to provide an extra 250 to 1000 mg. P/day for 4 to 8 weeks, maintained their normal calcium balance.

Ca/P ratios in food can now be safely forgotten, along with other once popular but now outmoded scientific fashions.

Fats.—Fatty acids form insoluble soaps with calcium. Thus fatty acids, and particularly those that are saturated, may carry into the fæces significant amounts of calcium, as occurs in the malabsorption syndrome. They may also carry with them fat-soluble vitamin D. Hence it is understandable how patients suffering from this syndrome may develop calcium deficiency.

Oxalic acid can inhibit the absorption of calcium because calcium oxalate is insoluble. Soluble oxalates are present in certain fruits and vegetables, but the amounts of these consumed are seldom sufficient to have any practical influence on calcium absorption.

The hydrogen ion concentration (*p*H) of the intestinal contents has often been considered a major factor determining the absorption of calcium, since calcium phosphate is precipitated in a slightly alkaline medium such as that provided by the digestive juices of the small intestine. It has been argued further that the absorption of calcium can only take place in the upper part of the small intestine, where the food is still mixed with the unneutralised hydrochloric acid of the gastric juice, which would keep the calcium phosphate in solution. The chief argument against this view is that patients with Addisonian anæmia and others who live for years with no gastric secretion of hydrochloric acid do not develop calcium deficiency.

COMMENT ON CALCIUM ABSORPTION

This summary of the factors known to affect calcium absorption shows that the problem is extremely complicated. There can be no clear answer that will explain why as much as 70 per cent. of the calcium in the food is normally excreted in the fæces. Obviously calcium absorption is not just a simple matter of the passage through the intestinal mucosa of free calcium ions, kept in solution by the benign influence of gastric juice, as many have believed. Other substances present in the food are clearly involved: on the positive side there are proteins and vitamin D, and against them, phytic acid and unabsorbed fatty acids. It may well be that other dietary factors affecting the particular form in which calcium ions meet the intestinal mucosa have yet to be discovered.

Output

Lactation

A lactating mother commonly loses 150 to 300 mg. of calcium daily in her milk. The mammary glands withdraw this amount from the blood which is simultaneously replenished with calcium either from the food or from the reserves in the bones. Normally the level of calcium in the serum is unaffected by lactation. This presents a remarkable example of the homœostatic powers of the body. The precise hormonal and enzymic mechanisms that maintain this homœostasis are still imperfectly understood. If the diet is grossly deficient in calcium, the bones must provide the calcium for the milk. However, in the whole period of lactation following the birth of a baby the total amount secreted would never exceed 100 g. of calcium, which is small by comparison with the total amount normally present in the bones. It is understandable, therefore, why there is usually no radiological evidence of loss of calcium salts from the bones during lactation, although in women previously seriously depleted of calcium, breast-feeding may precipitate the clinical features of osteomalacia.

Sudden decay of the teeth occurring during pregnancy and lactation is often attributed to decalcification; but if this is so, it is highly selective and perhaps represents a failure of the normal homœostatic mechanisms to draw first on the much larger reserves in the bones.

Excretion

In the fæces.—Most of the calcium found in the stools is the 75 per cent. or so of the dietary intake which, for one reason or another, never gets absorbed. The remainder is the amount 'excreted.' The probable origin of this amount is the quantity of digestive juices daily poured into the intestinal tract. Assuming this quantity to be about 8 *l.* and also that these juices have the same content of ionised calcium as the blood serum, 400 mg. Ca/day is likely to be secreted into the lumen of the bowel. The amount ultimately reabsorbed will depend on the various factors mentioned above which influence calcium absorption.

In the urine.—The urine normally contains 50 to 200 mg. Ca/day. This urinary excretion is the excess calcium left over from the amount absorbed from the gut, after the bones and soft tissues have taken up all that they can immediately accept.

CALCIUM BALANCE

An adult on a normal mixed diet is usually in a state of calcium equilibrium, *i.e.* the amount lost in the fæces and urine is approximately equal to the amount present in the food. Table 11, 4 gives the data of the measured calcium exchanges of three healthy individuals living on very different diets. The figures have been selected, from the large number of data available, to illustrate how calcium balance can be maintained on very dissimilar diets.

TABLE 11, 4. *Examples of calcium exchanges in healthy individuals*

(All figures in mg./day.)

Sources	Subject	Diet	Intake	Urine	Fæces	Total excretion	Balance
1	South African male	Normal mixed European	1008	135	858	993	+15
2	Bengali male	Rice and fish	536	80	395	475	+61
3	German boy aged 11	Orphanage diet: whole-meal bread and vegetables	944	43	509	552	+392

Sources: 1. WALKER *et al.* (1948). 2. BASU (1946). 3. WIDDOWSON & THRUSSELL (1951).

In growing children the body is normally in positive balance, with calcium being steadily retained for the formation of new bone. As the table clearly shows, when the need by the bones is great, net absorption of dietary calcium via the intestinal mucosa can be much greater than normal. This appears to be due to a mechanism regulating supply to requirements. A negative balance may occur in adults, *e.g.* when the extra output of lactation is not immediately met by an increased dietary intake, or when the customary amount of absorbable calcium in the diet is suddenly reduced. Negative calcium balance can also result from disturbances in one or more of the normal homœostatic mechanisms which regulate it.

ADAPTATION TO LOW CALCIUM INTAKES

Nicholls and Nimalasuriya (1939) showed that growing Ceylonese children often maintained a positive calcium balance on intakes of about 200 mg. Ca/day. Their observations have since been amply supported by observations made on citizens of such diverse places as Johannesburg (Walker & Arvidsson, 1954) Mysore (Murthy *et al.*, 1955) and Peru (Hegsted *et al.*, 1952). Walker and Arvidsson (1954) have shown that Bantus, receiving no more than 300 mg. Ca/day, have a normal level of calcium in the blood and, more important, normal amounts in their bones, as determined by chemical analyses of samples obtained both at operation and in the post-mortem room.

Malm (1958) has made a most thorough study of the adaption of 26 Norwegian prisoners to diets low in calcium. The subjects were healthy men aged 20 to 69 years, some of whom were investigated continuously for a year or longer. Table 11, 5 illustrates a metabolic study of a man in whom, after several months on a low calcium diet, the fæcal loss was so reduced that he was virtually in balance.

TABLE 11, 5. *An example of adaptation by a Norwegian to a low calcium diet* (*Case No.* 502, *Malm*, 1958)

(All figures in mg./day)

Days observed	Intake	Urine	Fæces	Balance	Total gain or loss
210	942	238	605	+100	+21 g.
210	436	200	323	−88	−18·5 g.
196	454	209	252	−7	−1·3 g.

Of the 26 subjects, 22 adapted satisfactorily, 10 rapidly and 12 slowly as in the example. One man made a slight adaptation, but in 3 there was no adaptation. These experiments leave no room to doubt that many Europeans can adapt to low calcium diets, but failure of a minority to do so would appear to justify the liberal recommended allowances of the N.R.C. and the B.M.A. (see p. 165).

These studies have been cited as examples of ‘ adaptation ’ to a low calcium intake. Perhaps it would be better to describe as ‘ maladapted ’ those adults who have grown accustomed over a long period to a calcium intake greatly in excess of their true needs, so that when their intake is suddenly reduced under the conditions of a short-term experiment they can no longer absorb enough calcium to keep themselves in equilibrium.

Regulation of calcium balance

The amount of calcium in the body is the result of a finely adjusted balance between intake and output. This balance in turn is determined by a further balance which exists between the amount of calcium in the fluids of the body and the large reserve in the calcium bank of the skeleton. It is beyond the scope of this book to discuss in detail the many factors that determine deposits and withdrawals of calcium from the bones ; they have been well described by Albright and Reifenstein (1948) and Greep and Talmage (1961). Three, however, deserve special mention.

The parathyroid glands influence the amount of calcium in the blood. In rare instances where these glands are overactive the osteoclasts are then stimulated to excessive activity with the result that calcium is withdrawn from the bones and the amount of ionised calcium in the blood rises. The total serum calcium exceeds 11 mg./100 ml.; it may rise as high as 20 mg./100 ml. Large amounts of calcium are excreted in the urine, and renal calculi composed of calcium salts may develop.

Sometimes the parathyroid glands are accidentally removed in the course of a surgical operation on the thyroid gland. As might be expected, parathyroidectomy results in a fall in ionised calcium in the blood with tetany as a frequent complication.

Vitamin D.—It has already been said that this vitamin facilitates the absorption of calcium from the gut. In recent years it has been established that vitamin D (in large doses at least) also has a direct effect in raising the serum calcium by causing resorption of bone (Barnicot, 1951), thus reduplicating some of the effects of the parathyroid hormone.

The kidneys play a crucial role in the maintenance of calcium balance by eliminating any excess present in the body fluids. Normally almost all of the ionised calcium passing through the glomerular filtrate is reabsorbed in the renal tubules. The factors that regulate the amount that finally escapes in the urine are complicated and imperfectly understood. There are rare kinds of renal failure in which tubular reabsorption of calcium is defective, with resulting osteomalacia (Chapter 30).

Recommended Allowances

Numerous experiments have been performed to determine the amount of calcium which the diet must provide in order to maintain calcium equilibrium. Most of these experiments, it should be noted, were carried out over short periods on adults accustomed to a good diet, rich in calcium. Sherman (1920*b*) in reviewing the literature up to 1920, estimated the average intake necessary for balance in such circumstances at 450 mg./day. Isabella Leitch (1937), in a detailed review of the subsequent evidence, raised the figure to 550 mg. Both of these authors were impressed at the time by the probability that osteoporosis, so common in old people, was due simply to lack of calcium in the diet. This view was challenged by Albright and Reifenstein (1948), but is again receiving support. It is discussed in Chapter 30. Sherman (1941) indeed believed that the ordinary mixed diet of Americans and Europeans was " more often deficient in calcium than in any other chemical element." His views no doubt weighed heavily with the Food and Nutrition Board of the National Research Council in the U.S.A. when, in 1941, it first recommended 0·8 g. as a suitable daily allowance for an adult, with larger amounts for adolescents and mothers with infants. Americans have always been generous, particularly in their ideas about food. In 1948 the N.R.C. raised the adult allowance to 1 g./day.

In 1950 the Committee on Nutrition of the British Medical Association decided that " there was not yet sufficient quantitative data to justify a departure from the National Research Council recommended allowances for calcium." However, in a conservative way, they kept the daily allowance for adults at 0·8 g. For children they recommended 1 g./day, rising to 1·4 g./day during adolescence, with 1·5 g./day during the latter half of pregnancy and 2 g./day during lactation.

In considering these recommendations it is essential to realise that they are based partly on the results of experiments conducted on individuals accustomed to a good Western diet (rich in calcium) and partly on well-informed guesswork. It would be wrong to assume that the recommendations of these committees represent the true needs of individuals throughout the world.

The FAO (1962) Committee on Calcium Requirements have suggested that a *practical allowance* for adults should be between 400 and 500 mg. per day. They add : " the usefulness of exceeding this has not been proved. In a number of countries the average daily intake is considerably higher, in some cases as high as 1500 mg. a day. There is no evidence that such a high intake is undesirable, but neither is there any indication that raising calcium intake above 1 g. will serve any useful purpose." The Committee recommends the following allowances for children and adolescents :—

Age	Practical Allowance mg. daily
0–12 months (not breast fed)	500–600
1–9 years	400–500
10–15 years	600–700
16–19 years	500–600

During pregnancy and lactation it is recommended that the allowance should be between 1000 and 1200 mg. a day. These recommendations are realistic for many countries.

The many factors regulating the absorption and excretion of calcium, and the balance between the two, have been outlined at some length in order to make clear how difficult it is to express calcium requirements in precise terms. In the present state of knowledge it is clear that the liberal recommended allowances are not a necessity for healthy bone development in many tropical countries ; yet it is generally agreed that if possible every child after weaning should have 500 ml. (about 1 pint) of cow's milk daily, which not only provides 600 mg. Ca but also other useful nutrients, including the amino acids that facilitate calcium absorption.

HYPERCALCÆMIA

In infants

Until recently it was generally assumed that any excess of calcium in the diet would fail to be absorbed by the gut and be rejected in the fæces. However, Lightwood (1952) of St Mary's Hospital, London, first described a new disease—idiopathic hypercalcæmia of infants. Since then the disease has been described in many other parts of Great

Britain and in Northern Europe, though it is much less common in the U.S.A. A full review of both the clinical and biochemical nature of the disease is given by Forfar and Tompsett (1959).

The disease usually starts between the ages of 5 and 8 months. The infants affected suffer from loss of appetite, vomiting, wasting, constipation, flabby muscles and a characteristic facial appearance. The level of ionised calcium in the blood is raised, as also is the blood urea, plasma cholesterol and blood pressure. Abnormal calcification may be present in the kidneys. The infants not infrequently die. Naturally there has been much speculation about the causation of this disease. Excessive absorption of calcium results from overdosage with calciferol, and many of the infants have received excessive amounts of vitamin D. In others there is no evidence of such overdosage. Perhaps these infants have some idiosyncrasy or hypersensitivity to the vitamin. It has been suggested (Forfar & Tompsett, 1959) that idiopathic hypercalcæmia may be due to a disorder of cholesterol metabolism, in which an excess of a vitamin D-like substance is produced. However, this is only speculation and as the term ‘ idiopathic ’ indicates, the cause is unknown.

Treatment consists of providing a diet as low as possible in calcium, and free from vitamin D. The commercial product, Locasol (Trufood Ltd.), is satisfactory since on reconstitution with water to a 12½ per cent. (1 in 8) solution, it provides a fluid which is similar to breast milk and has approximately the same composition in its content of protein, fat, carbohydrate and mineral. The calcium content, however, is not more than 60 mg. per pint as against 600 mg. per pint of milk. The preparation contains no vitamin D. It can be used as a beverage suitably flavoured and also in preparing soups, puddings and dishes permitted in the low calcium diet. After being on this diet for some months additional calcium may be allowed provided its effect on the blood calcium and on growth is carefully controlled.

In adults

Hypercalcæmia may also occur in adults as a result of hyperparathyroidism or through excessive intake or hypersensitivity to vitamin D. Burnett *et al.* (1949) have given an excellent account of the condition, arising from prolonged and excessive intake of milk and absorbable alkali for the treatment of peptic ulcer by patients with coexisting renal disease.

However, for the vast majority of mankind there is no danger of excessive calcium intake, since the homœostatic mechanisms of the body ensure that the amount of calcium retained from the food does not exceed the amount needed to replace the wear and tear of the bones and soft tissues.

Therapeutic Uses

When the bones are decalcified from an insufficient intestinal absorption of calcium, as in rickets, osteomalacia and the malabsorption syndrome, or when excessive calcium has been lost from the body, as in hyperparathyroidism or renal acidosis (Chapter 30), a large increase in the dietary supply of calcium is needed. In such cases plenty of milk or milk protein (*e.g.* cheese) should be the first line of treatment. But sometimes the immediate need for calcium is insufficiently provided by such natural sources. Fortunately soluble calcium salts appear to be absorbed from the gut just as readily. Calcium lactate or gluconate are the usual remedies. A level teaspoonful of calcium lactate weighs about 2 g. and provides 400 mg. of absorbable calcium. An effective therapeutic dose is three teaspoonfuls given three times a day in water before meals (providing about 3·5 g. of calcium). Calcium gluconate can be given intravenously in aqueous solution for the immediate relief of tetany.

PHOSPHORUS

The normal human body contains 600 to 900 g. of phosphorus, 80 to 85 per cent. of which is present in the bones where, in combination with calcium, it goes to provide their hard structure. The remainder is chiefly in the cells.

Physiology

Besides contributing with calcium to the physical support of the body, phosphorus is involved in a great variety of chemical reactions in the soft tissues, as discussed in previous chapters. Phosphate is the principal anion within the cells. It is an essential component of the nucleic acids. Many of the B group of vitamins are effective only when combined with phosphate in the body. The quick release of energy in muscles and nerves is affected by the breaking of high-energy phosphate bonds provided by adenosine triphosphate. In the breakdown of carbohydrates and fats, the formation of phosphate esters is an essential step (Chapter 9).

Phosphates in the blood.—As with calcium, a constant and well-regulated equilibrium normally exists between the phosphate stored in the bones and the amount circulating in the body fluids and therefore available to the soft tissues. The blood usually contains about 3·5 mg./100 ml. of inorganic P (normal limits, 2·5 to 4 mg.) which is present both in the red cells and serum. The constancy of this amount appears to be decided chiefly by the tubules of the kidneys which regularly reabsorb a large amount of the phosphate initially filtered by the glomeruli.

Deficiency of Phosphorus in Man ?

Phosphate is essential for all living processes ; perhaps for that very reason dietary deficiency of phosphorus is not known to occur in man. It should be noted, however, that phosphorus deficiency has been reported in cattle grazing on lands deficient in phosphate. All natural foods contain phosphorus because it is present in all living matter, whether plant or animal. The numerous forms in which phosphates occur in nature and their ready solubility (except those of calcium and inositol) account for the fact that they are absorbed with ease from the gut. Furthermore the kidneys are normally most efficient at retaining enough for all the needs of the body. Although the level of inorganic phosphate in the serum may be reduced in rickets, this is not due to any dietary deficiency but rather to excessive excretion in the urine under the stimulus of the parathyroid glands which respond in this manner to the shortage of circulating calcium.

DIETARY SOURCES

Phosphorus, as already mentioned, is present in all natural foods, though in refined and processed foods the phosphorus content may be greatly reduced (Table 17, 2). The best sources are those foods that also contain good amounts of calcium and protein. Phosphorus normally presents no problem for the dietitian. A useful working rule is, " take care of the calcium and the phosphorus will look after itself."

THERAPEUTIC USES

Proprietary preparations rich in phosphorus, made from burnt bones or containing glycerophosphates, have enjoyed a great vogue in the past as ' tonics.' The fact is, however, that additional phosphates by mouth have neither prophylactic nor therapeutic value.

TOXICITY

So far as is known, natural phosphates when taken by mouth in excessive amounts cause no harm ; probably they are simply voided in the stools. But elemental phosphorus itself is highly poisonous, as workers in the early match industry learnt to their cost. It causes an erosion of bone that used to be known as ' phossie jaw.'

MAGNESIUM

All human tissues contain small amounts of magnesium. The whole adult body contains about 25 g. or 2000 mEq. of the metal. The greater part of this amount is present in the bones in combination with phosphate and bicarbonate. Bone ashes contain rather less than 1 per cent. magnesium. It seems likely that the bones provide a reserve supply of magnesium, as of calcium and sodium, which is available when there is a shortage elsewhere in the body.

About one-fifth of the total magnesium in the body is present in the soft tissues, where it is apparently mainly bound to protein. The plasma normally contains 1·5 to 2 mEq./*l*. Next to potassium, magnesium is the predominant metallic cation in living cells. The concentration in the cells is about 15 mEq./*l.* and so there is a large gradient across the cell membranes. Inside the cells the metal appears to be concentrated within the mitochondria. It is an essential part of many enzyme systems responsible for the transfer of energy. For instance both co-carboxylase and co-enzyme A only act in the presence of traces of the mineral.

Fortunately, from the standpoint of the nutritionist, the maintenance of the body's supplies of magnesium is not a matter of practical difficulty. Most foods contain useful amounts of the metal, particularly those of vegetable origin, because magnesium is an essential component of chlorophyll. A typical British diet contains 200 to 400 mg. or 17 to 34 mEq./day (Duckworth & Warnock, 1942) which should be ample to maintain normal reserves. In contrast to calcium, vitamin D does not aid its absorption. Cereals and vegetables between them normally contribute more than two-thirds of the daily magnesium intake.

It is unlikely therefore that magnesium deficiency would ever arise in man from simple lack of foods containing it. On the other hand, the deficiency may occur under the same metabolic conditions that lead to a lack of potassium—excessive loss from chronic diarrhœa or from an intestinal fistula. Until recently magnesium deficiency in man has been overlooked ; this has been partly due to its close association with the better known features of calcium and potassium deficiency. Russell Fraser and his colleagues (Hanna *et al.*, 1960) have reviewed the literature and described three patients suffering from magnesium deficiency. The principal clinical features were depression, muscular weakness, vertigo and liability to convulsions. There were low voltage electrocardiographic changes. The plasma magnesium levels were all well below 1·5 mEq./*l.* and the diagnosis was confirmed by the prompt improvement which resulted from the administration of magnesium, 100–200 mEq. intravenously over 4 hours. Montgomery (1961) has shown that in kwashiorkor (Chapter 28) diarrhœa often causes depletion of magnesium in the cells ; biopsies of muscle in affected children showed that the magnesium content may be below 9 mEq./kg., less than half the normal figure. Magnesium deficiency may well contribute to the apathy and weakness which are characteristic of kwashiorkor. Now that scientific interest has been aroused and several accounts of the condition have been published, magnesium deficiency will probably be found to be not so uncommon as was previously supposed.

STRONTIUM

At the end of the eighteenth century, a mineral resembling heavy spar was found in the ore from the lead mines of Strontian in Argyllshire by Hope (1798). He wrote : " Considering it a peculiar earth, I thought it necessary to give it a name. I have called it *strontites* from the place where it was found, a mode of derivation, in my opinion, fully as proper as any quality it may possess."

Although widely distributed in nature and present in foods and in the skeleton, strontium aroused little interest amongst medical people until the start of atomic explosions. These produce radioactive isotopes of the element, which are widely dispersed in the 'fall out,' which follows the release of atomic and hydrogen bombs. The isotopes subsequently may become incorporated into plants and animals and so into human food. For further information about the hazards which may arise, see page 359.

Strontium, like calcium and magnesium, is a divalent metal belonging to group IIA in the periodic table (p. 152). The biological behaviour of the element is also in many ways similar to that of calcium. In general strontium is present in those foods which are rich in calcium, especially milk and to a lesser extent fresh vegetables; it is also stored in bone. Concentrations of strontium in biological material tend to be about one thousand times less than those of calcium and the microgram is the usual unit of measurement.

Widdowson and her colleagues (1960) have reported the results of balance studies on babies and have also discussed in this paper some aspects of strontium metabolism in adults. Cows' milk is richer than human milk in strontium as it is in calcium. These workers have shown that the intake of strontium was four to eight times greater in bottle-fed babies than breast-fed babies, that the amount of strontium retained was dependent on the quantity of milk ingested and that the breast-fed babies excreted more strontium than they were receiving. This was due to a large urinary output of strontium. In all infants, but more especially in those breast-fed, the ratio strontium : calcium was higher in the urine and fæces than in the bones. The body thus appears to discriminate against strontium in favour of calcium, especially in the newborn breast-fed infant.

SULPHUR

All living matter contains proteins and all proteins contain some sulphur; this element is therefore essential for life. The greater part of the sulphur in the human body is present in the two sulphur-containing amino acids, methionine and cysteine, or in the double form of the latter, cystine. Several enzyme systems, for example those containing co-enzyme A and glutathione, depend for their activity on free sulphydril (SH) groups. Sulphate ions are present in the cells and sulphate also occurs bound to various organic molecules. Of these the best known are the polysaccharides hyaluronic acid, heparin and chondroitin sulphate, already described in Chapter 4.

Two known vitamins, thiamine and biotin, contain sulphur. Sulphate esters of fatty acids are said to occur in the body, although practically nothing is known of their significance. The prefix *thio* (Greek : *theion* = sulphur) is used to denote certain compounds containing sulphur. Thiosulphate and thiocyanate have been detected in body fluids; the latter occurs in saliva, especially of tobacco smokers.

Metabolism of sulphur

Remarkably little is known about the daily turnover of sulphur in the human body, *e.g.* how much is normally ingested, how much excreted and the total amount present in the body at any one time. The principal reason for this ignorance is the lack of any simple method for estimating the element in human foods, excreta and tissues. No reliable metabolic balance studies on sulphur have yet been reported. Once such a method is perfected there is likely to be a great advance in knowledge of the part played by sulphur in human metabolism.

There is evidence that the sulphur-containing amino acids cannot be synthesised in the body and can only be obtained from the food. However, methionine, once it has shed its CH_3 group as a methyl donor, then becomes homocysteine, which, by combination with another amino acid—serine—is easily converted to cystine. Hence cystine and cysteine are not essential amino acids, so long as the diet provides sufficient methionine from which they can be derived in the body.

Sulphur is excreted in the urine. It appears partly as simple inorganic sulphate (about 0·5 g. S/day), and is partly combined with various organic molecules, one of which is indoxyl—a metabolic derivative of the amino acid, tryptophan. Indoxyl potassium sulphate (indican) is a substance that is easy to estimate in urine by virtue of its ability to form indigo blue when treated with ferricyanide. There is a large literature dating from the early part of this century, suggesting that indoxyl is a product of bacterial putrefaction in the gut, and that the sulphate attached to it assists in its ‘ detoxification.’ This is an obsolete notion ; it is no longer believed that metabolic disturbances are chiefly caused by bacterial toxins absorbed from the gut. The time is ripe for a new study of the origin of organic sulphates in the urine.

DIETARY SOURCES

It is generally supposed that the sulphur-containing amino acids are the chief source of sulphur in the diet, but this awaits proper investigation. Some foods, such as onions, contain sulphur in simple organic form that may well contribute to the nutrition of the body. It is even possible that the ancient nostrum of ‘ brimstone and treacle ’ had nutritional value unsuspected by modern knowledge.

EFFECTS OF DEFICIENCY

Presumably some of the effects of protein deficiency described in Chapter 5 are in fact due to failure of sulphur-containing enzymes, or even of the sulphur-containing polysaccharides described on page 52. But since protein deficiency itself is not a clear-cut clinical entity, it seems unlikely that sulphur deficiency will be identified by the clinician, unless he is aided by laboratory methods.

Recommended Allowances

Nothing is known of the sulphur requirements of man. It is not even known which foods ordinarily supply his needs. Judging from the sulphur content of different proteins, they are likely to be supplied mainly from animal sources.

IRON

The amount of iron in the body of a healthy adult is about 4 g. The major portion (about 2·5 g.) is present in hæmoglobin. This respiratory blood pigment has a complex molecular structure consisting of four polypeptide chains to each of which is attached a molecule of hæm, consisting of a porphyrin nucleus with an atom of iron in the centre. Myohæmoglobin also contains iron. It is a pigment, present in red muscle, which can easily take up or give off oxygen. In addition there are intracellular enzymes which contain iron porphyrins. Of these the most important are the cytochromes, which are widely distributed in cells.

Iron is an essential component of three different processes involved in the transfer of oxygen, and hence is of great importance in human nutrition. A deficient supply of iron is a very common cause of anæmia which is usually mild or moderate in degree. If the supply is gravely deficient for a long period a severe degree of anæmia may develop which may lead to a fatal result. Fortunately this is rare, for two reasons. First, the body conserves iron well ; the normal daily losses in the bile, fæces and sweat are small and the urinary excretion negligible. Secondly, in health a store of iron is maintained in the tissues. This amounts to 1 g. or more of the metal and is held in the tissues, bound to protein, in a form known as ferritin.

During the reproductive period of a woman's life additional losses of iron are inevitable. These occur at the menstrual periods and in the transfer of iron to the infant, when in the uterus and at the breast. There may also be a large loss of hæmoglobin due to hæmorrhage at labour. Thus, a woman during her reproductive life has a loss of iron at least double that of a man or of a woman after the menopause. If there are gynæcological disorders, the loss may be much greater. The intake of iron in the diet is often not able to meet this increased demand ; hence anæmia is very common in women in all countries of the world. It causes much ill-health and domestic unhappiness. It is also very common in infants and young children whose intake of iron in the diet is unable to meet the extra demands required for rapid growth.

The chief features of iron metabolism in man are set out in Fig. 11, 1.

Intake

The mean intake of iron in the diet by the population of the United Kingdom in 1959 was 13·9 mg./head/day. In all countries of the world people who eat a reasonably good diet obtain from their food at least 12 mg.

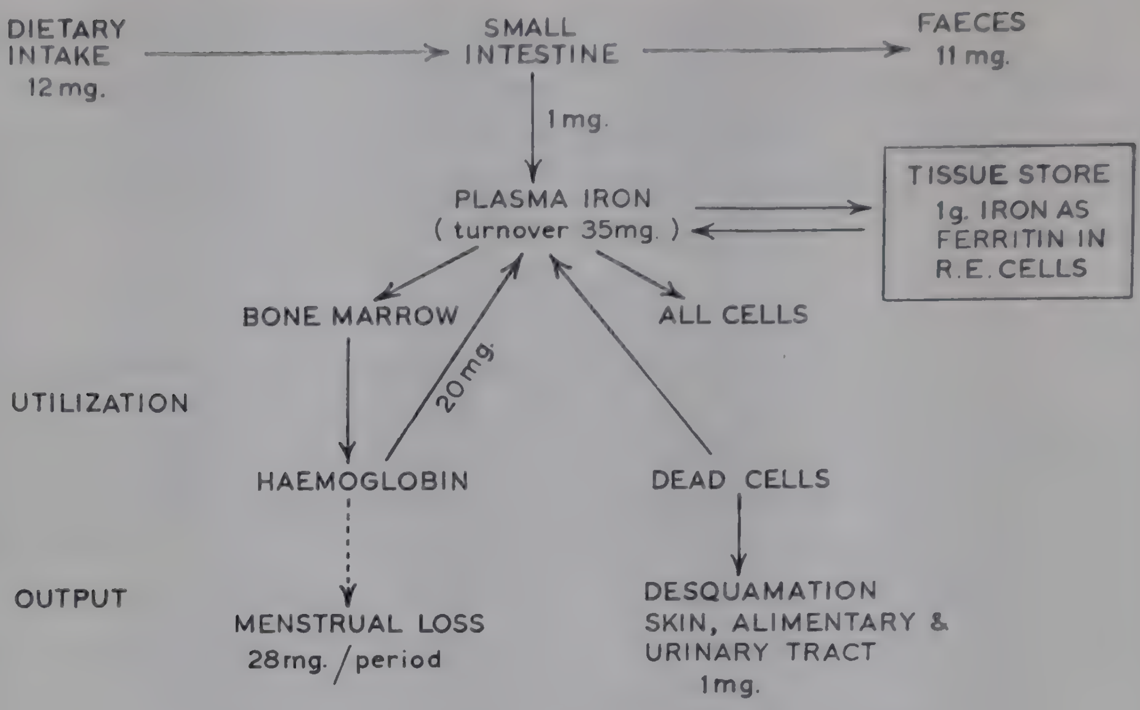

DIETARY INTAKE 12 mg.
SMALL INTESTINE
FAECES 11 mg.
1 mg.
PLASMA IRON (turnover 35mg.)
TISSUE STORE 1g. IRON AS FERRITIN IN R.E. CELLS
BONE MARROW
ALL CELLS
UTILIZATION
20 mg.
HAEMOGLOBIN
DEAD CELLS
OUTPUT
MENSTRUAL LOSS 28mg./period
DESQUAMATION SKIN, ALIMENTARY & URINARY TRACT 1mg.

FIG. 11, 1. Summary of iron metabolism in man.
(Adapted from MOORE, 1961.)

of iron a day and often much more. Table 11, 6 shows the iron content of some common foods. It will be seen that there is a wide range of values for each food. This depends in part on the soil and other conditions under which the foods were raised.

As, however, only a small proportion of the dietary iron requires to be absorbed to balance the daily losses, the factors determining absorption are in general more important than the total intake of iron.

ABSORPTION

Since the iron content of the body remains remarkably constant in health and only a small part of the dietary iron is absorbed, it follows that there must be a very fine regulatory mechanism controlling the absorption of dietary iron. This mechanism is not yet understood. For two decades it was widely taught that the amount of ferritin in the mucosal cells of the small intestine acted as a barrier which regulated the absorption of iron from the intestinal tract. This theory is no longer accepted, at least in its original form.

The study of the absorption of iron from the gastrointestinal tract has been greatly assisted in recent years by the use of ^{59}Fe, which can be identified subsequently in the blood and excreta by its radioactivity. The results of this experimental method have been excellently summarised by Moore and Dubach (1955) of the Washington School of Medicine, St Louis, who have been pioneers in this field. Besides using ferrous sulphate labelled with ^{59}Fe, Moore (1961) obtained foods containing radioactive iron by growing vegetables in nutrient solutions to which the isotope was added or by injecting iron into hens, chickens or rabbits so that eggs, liver and muscle contained the labelled iron. Dowdle *et al.* (1960) have studied the absorption of ^{59}Fe using sacs of small intestine from the rat. Active transport of iron from the mucosal to the serosal surfaces took place against a concentration gradient. This was dependent on oxidations and the consequent formation of phosphate-bond energy. Ascorbic acid markedly increased active transport of ^{59}Fe. By this and other techniques it has been demonstrated clearly that certain factors facilitate and others inhibit the absorption of iron.

TABLE 11, 6. *Iron content of some common foods*

For reasons described in the text, it is impossible to define precisely the 'availability' of the iron in a particular foodstuff.

Food	Description	Range (mg./100 g.)
Black (blood) sausage	...	20
Liver	Raw	6·0–14·0
Corned beef	Tinned	3·0–11·0
Beef, mutton	Raw, fresh	2·0–4·3
Fish	Raw	0·5–1·0
Eggs	Whole, fresh	2·0–3·0
Pulses	Various	1·9–14·0
Millets *	Various, raw	4·0–5·4
Oatmeal	Raw	3·8–5·1
Wheat flour	High extraction	3·0–7·0
Wheat flour	Low extraction	0·7–1·5
Cocoa	Powder	2·7–14·3
Chocolate	Plain	2·8–4·4
Treacle	...	9·2–11·3
Dried fruit	Various	2·0–10·6
Greens, leafy vegetables †	Raw	0·4–18·0
Potatoes and other root vegetables	Raw	0·3–2·0
Fruits	Tinned and fresh	0·2–4·0
Nuts	Various, without shells	1·0–5·0
Milk	Cow's, fresh whole	0·1–0·4

* *Cereals*, other than milled rice, may contain up to 9 mg. Fe/100 g. However, the associated high phytic acid content may reduce their value as sources of iron.

† *Green vegetables* commonly used in the tropics all fall in the upper part of the range and may therefore be useful sources of iron, while the vegetables (less green) most commonly used in temperate climates are generally from the lower part of the range and are consequently less important in their contribution to the iron content of the diet.

Facilitating factors.—Ferric iron is not absorbed, and iron in the diet has to be first reduced to the ferrous state before it can be transported across the gut wall. Absorption of iron is improved by the simultaneous administration of ascorbic acid. This is probably due to the reducing properties of the vitamin. Proteins may also assist iron absorption by virtue of the reducing properties of their –SH groups. Iron may also be carried across the mucosal cells chelated to amino acids or to ascorbic acid. The value of fresh vegetables or fruit in the prevention of anæmia probably lies more in their ability to facilitate iron absorption than in their actual content of iron.

Whenever there is a need for iron to make new blood, iron absorption is increased. This has been demonstrated in growing children and in pregnant women. Absorption is also increased both in man and in experimental animals when anæmia results from hæmorrhage. In averaging the overall results of 58 experiments in adult patients with iron deficiency, Moore found 20 per cent. of the ^{59}Fe was absorbed whereas in 133 experiments on control subjects considerably less than 10 per cent. was absorbed. These averages cover wide variations in individual experiments. Patients in the relapse stage of Addisonian anæmia absorb iron poorly, but immediately a hæmopoietic response results from the administration of vitamin B_{12} the absorption of iron becomes greatly increased.

Hence it seems reasonable to assume that when the rate of red blood cell formation is increased, a signal is sent to the small intestine to allow more iron to be transported across the mucosal cells to the plasma. Another factor which undoubtedly affects iron absorption is the amount of iron in the tissues. Neither the nature of the signal to the small intestine from the bone marrow or from the iron stores, nor the control system within the intestinal wall which regulates the absorption of iron is as yet known.

Inhibitory factors.—Phytic acid and other phosphates form insoluble salts with iron, as with calcium. This iron is thus unavailable for absorption. This is important in areas of the world where undermilled cereals which contain iron, but also much phytic acid, are the staple food. Thus in North India and West Pakistan a mild anæmia responding to iron therapy is not uncommon in young men. As Lehmann (1949) has shown, these men may be getting 22 mg. of iron daily from the whole wheat in their chapattis, far more than is present in a good Western diet; yet because of the high intake of phytic acid with the cereal and also perhaps a low consumption of fresh vegetables and ascorbic acid, inadequate amounts are absorbed. Absorption is also decreased when steatorrhœa is present.

Gastric acidity.—For many years it has been recognised that there is a close association between the incidence and degree of iron deficiency anæmia and a low level of gastric acidity. Hence it was taught that the acid secretion of the stomach facilitated the liberation of iron from bound forms in food and that the lowering of the *p*H in the small intestine helped the absorption of iron. These views have been challenged by Moore and Dubach (1951) who fed human subjects with food, such as chicken, eggs and green vegetables into which ^{59}Fe had been introduced during growth. The amount of radio-iron absorbed from these foods was not decreased when large quantities of antacid preparations, such as prescribed for patients with peptic ulcer, were added; nor was absorption increased when a meal of scrambled eggs containing ^{59}Fe was acidified with hydrochloric acid so that the *p*H was 1·5. These findings are contrary to those reported by Kellog and Mettier (1936) and by Heath and Patek (1937).

In conclusion it may be stated that the effect of gastric acidity on the absorption of iron is a highly controversial subject. Lack of gastric acidity can only be one of the factors concerned in the causation of chronic nutritional iron deficiency anæmia (Chapter 36), because it is well known that some anæmic patients secrete a normal amount of hydrochloric acid while other people may have achlorhydria for many years and yet maintain a normal hæmoglobin level.

Although a decrease in the absorption of iron which may result from achlorhydria may be of little importance to males or post-menopausal women whose requirements of iron are small, it may play a significant role in the production of anæmia in women of the child-bearing age whose requirements are high.

IRON TRANSPORT

Iron is absorbed into the blood stream and not into the lymph. In the blood it is carried bound to a protein known as transferrin ; this is a specific plasma protein belonging to the *beta* globulin group. Normal plasma contains about 0·25 g. of transferrin/100 ml. This gives the plasma a total iron binding capacity (TIBC) of about 300 μg. of iron/100 ml. The TIBC is increased when the need for iron is increased as in the later stages of pregnancy, in iron deficiency anæmias and in siderosis. Decreased values are found in infections, uræmia and liver failure and in hæmorrhagic anæmias. Normally the TIBC is not fully saturated, and in health the plasma contains about 100–150 μg. of iron/100 ml. In iron deficiency the level is much lower and the degree of unsaturation very much greater.

The transport system has to deal with some 20 mg. of iron daily liberated from broken-down red cells and also an additional amount of absorbed iron going to and from the cells and the storage depots. The daily turnover of plasma iron is about 35 mg. Only a very small proportion of this originates from the diet, even when iron absorption is at a maximum.

UTILISATION

Most of the iron utilised by the body is needed by the bone marrow to make hæmoglobin for new red blood corpuscles. The life of a red blood corpuscle is about 120 days. It is then destroyed, the hæmoglobin broken down and the iron liberated. For this reason 1/120 of the total hæmoglobin in the body has to be replaced daily in the bone marrow. This involves an uptake of about 20 mg. of iron from the plasma.

The intracellular iron present in all cells is also being constantly turned over. The total amount of this *tissue iron* is only about 300 mg., but a significant amount must be replaced daily to make good the losses in dead or desquamated cells.

STORAGE

Iron combines with a protein to form a complex compound, ferritin, which is normally stored in the fixed phagocytic cells of the reticulo-endothelial system, chiefly in the liver, spleen and bone marrow. The normal amount of iron in this store is about 1 g. It is only turned over slowly and hence is not immediately available for increased hæmoglobin synthesis if this is needed urgently, as after a severe hæmorrhage.

The storage iron may be greatly increased ; if this occurs the ferritin molecules become conglomerated and form a substance, hæmosiderin. This can be readily detected in tissue because on addition of ferricyanide a blue colour (Prussian blue) is formed which can be easily seen with the naked eye.

Siderosis.—This term is used to describe the presence of excess iron in the body, as demonstrated by the presence of hæmosiderin in the tissue. Excess iron accumulates in the tissue of patients with all types of hæmolytic anæmia. In these disorders the red blood corpuscles are broken down more rapidly than normal. Severe anæmia may result, requiring repeated blood transfusions to prevent incapacity or even to save life. Since the iron liberated from the destroyed cells is not excreted and since each 500 ml. of blood transfused contains over 200 mg. of iron, a considerable accumulation may occur in the stores.

There is also a rare disease, hæmochromatosis, in which excessive amounts of iron are absorbed from the alimentary canal. The metal is deposited chiefly in the liver and spleen, but also in the pancreas, skin and many other organs, giving rise to various disorders including cirrhosis of the liver, diabetes mellitus, and sometimes a leaden-grey discolouration of the skin. This failure of the control mechanism in the alimentary canal is probably due to a genetic defect.

Nutritional siderosis.—It is now well known that siderosis is common amongst the Bantus in South Africa. Bothwell and Bradlow (1960) measured the iron content of 147 livers from Bantus who had died from accidents. In all but 16 the normal maximum (100 mg./100 g.) was exceeded. With a slight overload all the iron was present in the parenchymal cells, but with increasing concentrations it also appeared in the Kupffer cells and in the portal tracts. Here the excess iron may set up fibrosis and perhaps lead to cirrhosis of the liver.

The Bantus cook their maize and other cereals in iron pots. Some of the iron gets into the food and as much as 100 mg. or more may be ingested daily. The gastrointestinal tract may fail to reject this large extra intake for reasons that are not clear. This failure may perhaps be secondary to faults in the diet. There is evidence from animal experiments which indicates that a poor unbalanced diet, especially one inadequate in protein, facilitates the absorption of excess iron in the diet. For a fuller account of nutritional siderosis the reader is referred to papers by Bothwell and Bradlow (1960), by Gillman *et al.* (1959), and by Goldberg and Smith (1960).

It is not yet clear whether this condition, which is very common in its minor forms, affects the health of the Bantu population significantly.

OUTPUT

The crucial fact that the iron liberated by the continuous breakdown of red blood corpuscles is not excreted but conserved and utilised was first demonstrated by McCance and Widdowson (1937). Neither the kidneys nor the cells of the intestinal and sweat glands appear to have the power to concentrate iron. In consequence the iron content of their cell-free secretions is not higher than that of plasma and the total loss in this way is very small (0·5–1 mg. daily).

Samples of sweat rich in cells have been found to contain 1·6 mg. Fe/1 (Hussain & Patwardhan, 1959). If concentrations in sweat were always of this order, the inhabitants of the tropics would lose large amounts of iron in this way. It is probable that the experimental procedures used in procuring samples of sweat may lead to a great increase in the shedding of desquamated cells, and that natural sweat usually does not contain such large numbers of cells. The matter is not yet settled, but it is doubtful if losses of iron in the sweat are an important cause of iron deficiency anæmia in the tropics.

Most of the iron in the fæces has, of course, never been absorbed into the body. Losses in menstruation and during pregnancy and lactation are further discussed in Chapter 36.

RECOMMENDED ALLOWANCES

The National Research Council of the U.S.A. in 1948 recommended a daily intake of 12 mg./day for adults, with extra allowances during adolescence and pregnancy (Table 15, 2, p. 255). This figure is based on the observation that healthy people eating a good mixed diet containing 12 mg. iron/day are not anæmic. If anæmia develops in such people there must be a chronic loss of blood from hæmorrhage from some site. The Committee on Nutrition of the British Medical Association in 1950 adopted this recommendation, although recognising that " a great deal about iron requirements of the human body remains to be discovered."

Although a normal adult male living in a temperate climate loses at most 1 mg. Fe/day, the loss may be very much greater, as a result of chronic bleeding, or in women from menstruation or pregnancy as described in Chapter 36. In such circumstances a diet providing 12 mg./day may prove insufficient even though it may appear satisfactory in respect of the other nutrients mentioned above which influence the absorption of iron.

THERAPEUTIC USES

Fortunately the treatment and even the prevention of iron deficiency anæmia is not dependent on dietary means. Ferrous salts by mouth are cheap and effective, as discussed in Chapter 36. In certain pathological conditions (*e.g.* the malabsorption syndrome, p. 508) ferrous salts taken by mouth may be ineffective. In such cases saccharated oxide of iron can be administered intravenously, with excellent effects.

Toxic Effects

Accidental poisoning with ferrous sulphate, usually in children, has sometimes been fatal. It does not appear, however, that the symptoms of which patients complain when taking therapeutic doses of iron are simply milder forms of those caused by acute poisoning, since the latter are partly due to excessive absorption of iron (Reissman *et al.*, 1955). For instance, constipation is the most common complaint of patients taking iron, whereas diarrhœa is an almost constant feature of ferrous sulphate poisoning.

Ferrous sulphate is widely believed to cause more toxic reactions than the new organic preparations, such as ferrous gluconate and ferrous succinate, but this is not borne out by a critical study of the published records of patients receiving different iron preparations but with a similar content of elemental iron. Toxic symptoms were reported in 4 per cent. of 367 patients receiving an average of 220 mg. of ferrous sulphate daily, while a similar incidence occurred in patients receiving 210 mg. of ferrous gluconate daily. In trials carried out by Kerr and Davidson (1958*a*) on antenatal patients and on healthy non-pregnant young women, pills containing various preparations of iron with identical coating and the same iron content, and similar control pills without iron were given to matched groups of patients on the ' double blind principle.' Neither the patient nor the doctor knew which preparation was being employed until the results were assessed. These trials showed no significant difference in the incidence of toxic effects between the different preparations of iron tested or between the iron pills and the control pills containing lactose. Hence it was concluded that intolerance to iron preparations is largely psychological in origin.

Experience has shown that reassurance and enthusiastic propaganda will do much to reduce the ' intolerance rate.' In addition, all patients taking iron pills should be instructed to take them after meals. If this is done, only a small proportion of patients will be unable to take ferrous sulphate, which is much cheaper and just as effective as the more expensive iron preparations.

CHAPTER 12

MINERALS: (2) TRACE ELEMENTS

IT is a convenient custom to group together under the general heading of 'trace elements' those metals and non-metals that are regularly present in very small amounts in animal tissues and known to be essential for normal tissue metabolism.

Sir Joseph Barcroft (1944) defined a trace element as one that occurs in not more than one part in twenty thousand of the organism and is concerned in some way with enzymic actions. The first part of this definition excludes iron from the list, although some authors include it among the trace elements. More usually the list is confined to copper, cobalt, zinc, manganese and iodine. Some doubt exists about three other elements.

Molybdenum has been demonstrated in the tissues of various species of animals. The enzyme xanthine oxidase has been shown to be a molybdoflavoprotein. There is every probability therefore that molybdenum is a necessary nutrient for man, although this is not yet proved. An excessive intake of molybdenum in cattle and sheep causes diarrhœa ('teart').

Nickel has been shown to be present in human liver and pancreas. Its close similarity to cobalt in chemical properties suggests that it might have some essential enzymic property in animal tissues; so far, however, none has been demonstrated. Nickel alloys are widely used for lining cooking vessels, pasteurisation equipment, etc. A nickel catalyst is used in the hydrogenation of oils for making margarine. Very small amounts of adventitious nickel may be ingested from these sources, but there is no evidence at present that this is a hazard to health.

Fluorine has not yet been proved to be an indispensable nutrient for any species of animal. However, its regular presence in minute amounts in human bones and teeth, and its important influence in the prevention of dental caries (p. 188), justify the inclusion of fluorine in the following pages.

An excellent monograph on the trace elements has been written by Underwood (1956).

COPPER

PHYSIOLOGY

All tissues in the human body contain traces of copper; the total amount in an adult is 100 to 150 mg. There are good reasons for thinking that its presence is not merely fortuitous. Copper is an essential nutrient for many species of animals. Many invertebrates have a copper-containing respiratory pigment—hæmocyanin—which seems to subserve much the same purpose as does hæmoglobin in the vertebrates. The turaco, a South American bird, has a green pigment in its feathers that is partly washed off in wet weather. This pigment is a copper-containing porphyrin ; the discovery of its chemical nature was an important milestone in the history of porphyrin chemistry.

Copper, like iron, is one of the transition elements with a dual valency which makes it a valuable catalyst in the chemical industry and also, most probably, in oxidation-reduction mechanisms of living cells. It is an attractive theory that the course of animal evolution has been influenced decisively by the success or failure of natural experiments in the use of transition elements as respiratory catalysts. So far as is known, only the sea-squirt uses vanadium, which perhaps explains its present lowly position in the animal world. Although iron has largely replaced copper in the respiratory mechanisms of the vertebrates, there is good evidence that even the higher mammals still have a use for copper. Certain essential enzyme systems, including those responsible for the oxidation of ascorbic acid, seem to be dependent on catalytic traces of copper. The study of the precise mode of action of copper in isolated animal tissues has been hampered by the technical difficulty of estimating it in very small amounts, and also by the fact that almost all biochemical reagents and apparatus already contain traces of the metal.

Copper Deficiency in Animals

In certain mountainous areas (*e.g.* in Scotland) lack of copper in the soil and grass affects the sheep that graze there. The lambs are often born dead or, if they survive, suffer from a demyelinating disease of the spinal cord known as ' swayback ' which results in ataxia. This condition has been extensively studied by Underwood (1953) in Australia where the same problem exists. Cattle grazing on copper-deficient pastures often suffer from chronic diarrhœa (' scours ').

Anæmia is a common, but not constant feature of copper deficiency in sheep and cattle although it can be produced regularly by this deficiency in rats. Cartwright (1955) has shown that experimental copper deficiency in pigs produces a marked fall in serum iron despite an ample iron intake. Both the absorption and utilisation of iron is impaired, producing an anæmia resembling that of iron deficiency.

Copper in Human Nutrition

So far there is no evidence that dietary deficiency of copper ever occurs in man. Indeed the wide distribution of traces of copper in even the poorest of human foods, and the very small amounts that are normally present in the body, make it inherently unlikely that such a deficiency could ever arise. Infants are born with an apparently ample store; their bodies contain proportionately more copper than the adult body. A normal diet for an adult in Great Britain contains about 2 mg. Cu/day (Tompsett, 1954).

PATHOLOGY

Nevertheless there can be no doubt that copper is an essential nutrient for man. Traces are normally present in the blood in combination with an α-globulin to form a blue-coloured protein, cæruloplasmin. For some unknown reason the concentration of this protein, in common with the 'C-reactive protein,' is elevated in infective and rheumatic disorders, and also in pregnancy (Cartwright & Wintrobe, 1955).

A disorder of copper metabolism is involved in the rare disease first described by Kinnier Wilson in 1912. In this condition the cæruloplasmin is much reduced owing to a genetic defect. There is also for some unexplained reason increased copper absorption from the gut. Copper accumulates in the tissues, most markedly in the liver and in the grey matter of the brain, especially the lenticular nucleus. This process appears to go on from birth and after several years leads to cirrhosis of the liver and severe nervous disorders (hepatolenticular degeneration).

THERAPEUTIC USES

The authoritative opinion of Cartwright (1955) is that copper is unnecessary in the therapeutic armamentarium of the clinician.

TOXIC EFFECTS

Copper sulphate is widely used for killing algæ and bacteria in swimming pools, etc., but in high concentrations at least, it is poisonous to animals and man. A concentration of 1·5 parts per million should not be exceeded in drinking water.

COBALT

The discovery in 1948 that cyanocobalamin contains 4 per cent. of cobalt (p. 238) established for the first time that this metal is an essential nutrient for man. It had been known previously that cattle and sheep grazed on pastures deficient in cobalt develop a wasting disease known as 'pine,' characterised by loss of appetite, debility, anæmia and emaciation. Ruminant animals need traces of cobalt in their diet, probably to enable the bacteria in their rumen to synthesise cyanocobalamin. Attempts to produce experimental cobalt deficiency in animals with dietary habits more closely resembling the human—such as the rat and the pig—have consistently failed to produce any recognisable disorder.

If, as seems likely, cyanocobalamin is the only cobalt-containing compound regularly present in human tissues, the quantity of the metal needed to maintain the body in health is extremely small, since the total amount of cyanocobalamin in the whole body is about 2 mg.

Traces of cobalt are present in a great variety of foods, in cooking utensils and even in the atmosphere, at least in industrial cities ; it is therefore most unlikely that cobalt deficiency could ever arise in man.

Cobalt chloride has been given to patients with a variety of refractory anæmias. There is as yet no satisfactory evidence that any permanent benefit has followed, and in the dosage used cobalt can have unpleasant toxic effects (Gairdner *et al.*, 1954).

ZINC

Normal human blood (Vallee & Gibson, 1949) contains about 1 mg. Zn/100 ml. ; the greater part of this amount is contained in the erythrocytes where it forms an essential component of the enzyme carbonic anhydrase, which catalyses both phases of the reaction $H_2CO_3 \rightleftharpoons CO_2 + H_2O$. Both the zinc and carbonic anhydrase content of the plasma were found (Vallee & Gibson, 1949) to be reduced in 29 patients with miscellaneous anæmias. The content of the red blood corpuscles was normal, except in those from patients with Addisonian anæmia. In these it was significantly above normal.

Traces of zinc are also regularly present in other human tissues, including the pancreas. Insulin extracted from the pancreas of animals for the treatment of diabetes mellitus regularly contains about 0·3 per cent. of zinc. Some part of the normal insulin secretion of the pancreas may have a delayed action akin to the artificial insulin-zinc preparations.

There is therefore good circumstantial evidence for regarding zinc as an essential element in the economy of the human body and thus as a necessary nutrient. However, dietary deficiency of zinc has so far been produced experimentally only in the rat ; it has not been described in any other animal, including man. Most human diets contain 10 to 15 mg. Zn/day, which is probably more than enough to provide for all ordinary human needs, even allowing for limited absorption in the gut.

MANGANESE

Traces of manganese have been shown to be present in human blood and also in the liver. Although there is still no direct evidence that the metal plays any useful role in human metabolism, and is therefore needed in the diet, there is much circumstantial evidence for believing this to be true. Manganese deficiency has been produced experimentally in other mammals, such as the rat, rabbit and pig. The chief result is defective growth in the length of the long bones, apparently because traces of manganese are needed for the proper activity of the enzyme, alkaline phosphatase. Manganese also activates another enzyme, arginase, on which the formation of urea in the liver depends. Lack of manganese in chickens results in a deformity of the legs (perosis) due to slipping of the Achilles tendon at its point of attachment.

Normal human diets of the Western type contain 5 to 10 mg. Mn/day, the greater part of which is eliminated in the fæces. Curiously enough, tea is an especially rich source of the metal.

Cases of manganese poisoning have been reported in men mining or preparing manganese ore. The clinical picture resembles that of Wilson's disease (Turner, 1955).

IODINE

Iodine (atomic weight, 127) is the heaviest element known to be essential for the metabolism of human tissues. The adult body normally contains 20 to 50 mg. of iodine ; about 8 mg. of this amount is concentrated in the thyroid gland. Since the thyroid normally weighs only 0·2 per cent. of the whole body it is evident that this concentration is intense. Iodine is contained in the hormones stored and secreted by the gland.

History

Iodine was first discovered in 1811 by Courtois, who was working in Paris to keep Napoleon supplied with gunpowder. He used kelp (dried seaweed) as a source of lye for the manufacture of nitre and found the iodine in it. The chemical properties of the new element were investigated by Gay-Lussac and by Sir Humphry Davy who—by the personal permission of Napoleon—was passing through Paris on his way to Italy at the time. Andrew Fyfe of Edinburgh in 1819 was apparently the first to demonstrate its presence in the animal body. In 1820 the Geneva physician, Coindet, successfully treated goitrous patients with tincture of iodine. This was enthusiastically pursued by several French and Swiss investigators, notably by Chatin of Paris. Chatin carried out extensive and surprisingly accurate analyses of iodine in foodstuffs and drinking waters and came to the conclusion that although the element is universally distributed in nature, it is relatively deficient in areas where goitre is endemic. He provided the first sound scientific backing for the belief that goitre is due to deficiency of iodine. In 1860 Boussingault instigated an experiment on the use of iodine in the prevention of goitre among school children in three areas of France. Unfortunately the dose given was far too large and toxic effects were observed. This brought discredit on the whole idea. Soon afterwards the mounting enthusiasm for bacteriology, engendered by Pasteur, sent the medical profession on a false trail in pursuit of an infective cause for goitre. Nevertheless many humble people suffering from goitre continued to take iodine as a secret nostrum.

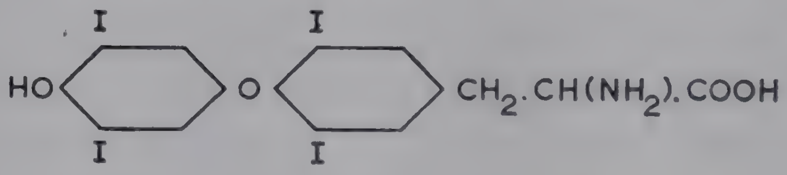
Interest in iodine was revived when Baumann (1895), of Freiburg in the Black Forest (a goitre area), discovered that the thyroid gland contains iodine. Thereafter the Americans began to take up the trail. Marine and Lenhart (1911) found that goitre in trout could be prevented with iodine ; Marine and Kimball (1920) published the results of their classic experiment in school children in Akron, Ohio, which succeeded in proving what the French had failed to show a generation before—that sodium iodide in suitable doses reduces the incidence of goitre in children. Their results were confirmed and enthusiastically supported by numerous doctors in Switzerland.

Meanwhile Kendall and Osterberg (1919) in America, after much painstaking work in the laboratory, succeeded in isolating from thyroid glands a crystalline iodine-containing compound which they called ‘ thyroxine.’ Sir Charles Harrington (1926) first correctly determined the chemical structure of thyroxine and in the following year successfully accomplished its synthesis in collaboration with Professor G. Barger of Edinburgh (1927). Gross and Pitt-Rivers (1952) demonstrated the presence of another hormone—tri-iodothyronine in the thyroid gland.

Physiology

All vertebrate animals require iodine and they all possess thyroid tissue in some part of the body. This tissue has the specific property of taking up iodine, storing it, and subsequently releasing it in controlled amounts in the form of thyroid hormones. Iodine is unique among the necessary mineral elements in that it is an essential component of specific hormones.

The iodine in food and water is quickly absorbed from the alimentary canal. In the blood it is present mostly as inorganic iodide ; a proportion of this is taken up by the thyroid gland, the amount depending on the activity of the gland. In the gland the iodide is oxidised to iodine, which is immediately bound to tyrosine with the formation of mono- and di-iodotyrosines. These substances are subsequently converted into thyroxine and related hormones. This takes place in the epithelial cells of the gland. Thyroxine is then bound to a globulin to form thyroglobulin in which form it is stored in the vesicles of the gland. From the gland it is released, as required, into the blood stream loosely bound to an alpha globulin. With a normally active gland the level of this protein-bound iodine (PBI) in the plasma lies between 3 and 8 μg./100 ml.



The output of thyroid hormone is controlled from the pituitary gland by means of the thyrotropic hormone.

The thyroid secretions control the level of metabolism in many cells. If the secretion is deficient, the basal metabolism falls, the circulation is reduced and the whole tempo of the patient's life is slowed down.

The secretions also control in some way the state of the connective tissues. A lack of the hormone causes the accumulation of mucopolysaccharides under the skin and in other organs. This coarsens the features and gives the patient suffering from thyroid deficiency a characteristic appearance (myxœdema).

The part played by lack of iodine and other dietary factors in causing enlargement of the thyroid gland (goitre) is discussed in Chapter 55.

Sources

In view of the widespread distribution of iodine in living matter and the very small amounts needed by the human body, it is not surprising that it is difficult to discover which foodstuffs ordinarily supply the iodine normally present in the healthy human body. However, fish, vegetables and milk are normally useful sources. Any attempt to give precise figures for the iodine content of different foods for inclusion in Tables of Food Values is clearly unrealistic, since the values vary very widely from one locality to another, depending on the iodine content of the soil on which the foods were raised. Much attention has been directed in the past to the iodine content of drinking waters in areas where goitre occurs, as compared with the waters in goitre-free districts. As a result there has been a tendency to regard drinking water as an important source of iodine. But, in fact, fresh water usually contains only small amounts of iodine, *e.g.* 1 to 50 μg./*l.* in Great Britain (Murray *et al.*, 1948), so that it contributes little to the needs of the body. The iodine content of the water in a locality is more important as an index of the amount of iodine that is likely to be provided by the cereals and vegetables that grow in the soil which the water irrigates. Among people who live largely on imported food it is a matter of little consequence. Contrary to usual belief, sea water is a relatively poor source of iodine, containing less than 20 μg./*l.*

The isotope ^{131}I is part of the fall-out from nuclear explosions. Cattle concentrate it from grass and secrete it in milk. The hazards are discussed in Chapter 24.

Recommended Allowances

Attempts have been made in the past to define ' requirements ' for iodine. Various figures have been proposed, ranging from 50 to 300 μg./day for the requirements of an adult. But such figures are based on scant evidence ; moreover they are unrealistic, since the true requirements obviously vary very much, even within the physiological range. The need for iodine is influenced by a multitude of normal dietary and environmental factors such as the amount of cabbage and other *brassicæ* eaten, the hardness of the drinking water, the climate, the age and activity of the people and their exposure to infections or other stresses. These factors are further discussed in connection with goitre in Chapter 55.

Prophylactic and Therapeutic Uses

Small doses of iodine are of great value in the prevention of goitre in areas where it is endemic, and may be of value in treatment, at least in its earliest stages. Larger doses have a temporary value in the preparation of patients with hyperthyroidism for surgical operation. Tincture of iodine formerly enjoyed a vogue as an antiseptic for surgical wounds and skin lesions, but has now been replaced by more effective bactericidal agents.

Toxic Effects

Excessive amounts of iodides taken by mouth irritate mucous membranes and the skin, producing rashes and other toxic manifestations.

FLUORINE

In 1805 Gay-Lussac first detected fluorine in the animal body. Traces of this element are regularly present in human tissues, notably in the bones, teeth, thyroid gland and skin. There is now no doubt that traces of fluorine in the teeth help to protect them against decay, yet there is no evidence that fluorine is indispensable in other tissues. Attempts to produce experimental fluorine deficiency in animals have repeatedly met with failure.

Sources

Most human adults ingest between 2 and 3 mg. of fluorine daily. The chief source is usually drinking water, which, if it contains 1 part per million (p.p.m.) of fluorine, will supply 1 to 2 mg./day. Soft waters may contain no fluorine, whilst very hard waters may contain over 10 p.p.m. Compared with this source, the fluorine in foodstuffs is of little importance. Very few foods contain more than 1 p.p.m.; the exception is sea-fish which may contain relatively large amounts of the order of 5 to 10 p.p.m. Another significant source is tea, particularly China tea, which in the dry state may contain as much as 100 p.p.m. In Britain and Australia, where people are addicted to tea, the adult intake from this source may be as much as 1 mg. daily.

It is worth noting that the fluorine content of most plants bears little relation to the amount of fluorine in the soil on which they are grown; plants seem to be selective in the amount they absorb.

Use of Fluorine in the Prevention of Dental Caries

Epidemiological studies in many parts of the world have established beyond doubt that where the natural water supply contains fluorine in amounts of 1 p.p.m. or more, the incidence of dental caries is lower than in comparable areas where the water contains only traces of the element.

Fluorides become deposited in the enamel surface of the developing teeth of children. Such fluorotic teeth are unusually resistant to caries for reasons not yet fully understood ; it may be that traces of fluorine in the enamel discourage the growth of acid-forming bacteria ; alternatively, the calcium phosphate of the enamel may be rendered more resistant to organic acids by combination with traces of the element. It should be noted that fluorine is not deposited in fully developed adult teeth, so that no benefit to adults can be expected when they begin for the first time to drink water containing traces of fluorine.

The deliberate addition of traces of fluorine to those public water supplies which are deficient in fluorine is now a widespread practice throughout North America where 32 million people are drinking water mechanically fluorinated. In at least 17 other countries similar projects have been started.

In the United Kingdom fluoridation of the water supply up to 1 p.p.m. was begun in three experimental areas, Anglesey, Kilmarnock and Watford, in 1956. Three neighbouring areas in which the water was unchanged served as controls. A dental survey of the children was carried out then and again in 1961 (Ministry of Health, 1962). Larger numbers of children were involved in this very careful study. Table 12, 1 summarises the results. There can be no doubt that in the three areas where fluorine was added to the water, a substantial reduction in caries followed. In view of the widespread incidence of caries throughout the United Kingdom, the case for the addition of fluorine up to 1 p.p.m. to the water supplies of those areas where it is lacking, is strongly supported by these trials.

TABLE 12, 1. *Average number of carious teeth per child*

Children's ages	Control areas		Areas with water to which fluorine was added		Percentage reduction
	1956	1961	1956	1961	
3 years *	3·53	3·32	3·80	1·29	66
4 years *	5·18	4·83	5·39	2·31	57
5 years †	5·66	5·39	5·81	2·91	50
6 years †	6·32	6·22	6·49	4·81	26
7 years †	7·08	6·89	7·06	6·05	14

* Full dentition. † Deciduous canines and molars only.

TOXIC EFFECTS

Fluorine in excessive amounts is a powerful inhibitor of cell metabolism, and is thus poisonous in large doses.

Fluorosis in animals.—Outbreaks of fluorine poisoning have been described in cattle and sheep, and are liable to occur whenever the vegetation on which they graze is contaminated by fluorine-containing dust. A notable outbreak was caused by the eruption of Mount Hekla in Iceland in 1845 (Roholm, 1937). Smoke from brick kilns in England and from the aluminium works at Fort William in Scotland (Agate *et al.*, 1949) have likewise caused fluorosis in livestock.

The first sign of fluorosis is usually seen in the teeth of young growing animals, which are mottled with white patches and present a rough enamel surface. In adult animals the first effect is generally the development of bony changes. The surfaces of the long bones and lower jaw become thickened and densely calcified, often with bony outgrowths (exostoses). The animals become weak and their milk yield is reduced.

Fluorosis in man.—In many parts of the world where the fluorine content of the water is high (over 3 to 5 parts per million) mottling of the teeth is common. The enamel loses its lustre and becomes rough. Bands of brown pigmentation separate patches as white as chalk. Small pits may be present on the surface (Plate XX, C). All the teeth may be affected, but mottling is usually best seen on the incisors of the upper jaw. Dental fluorosis is not usually associated with any evidence of skeleton fluorosis or indeed with any impairment of health.

Chronic fluorine poisoning has been reported in several localities in India, China, Argentina and the Transvaal, where the water supply contains over 10 p.p.m. fluorine. Fluorine poisoning has also occurred as an industrial hazard among workers handling fluorine-containing minerals such as cryolite, used in smelting aluminium. The effects are much the same as in animals ; there is loss of appetite and an increased density (sclerosis) of the bones of the spine, pelvis and limbs. In addition the ligaments of the spine becomes calcified, producing a ' poker back,' resembling the condition called spondylitis ankylopoietica. There may also be ossification of the tendinous insertions of muscles, producing characteristic ' rose-thorn ' shadows in the radiograph (Hunter, 1955). Neurological disturbances secondary to the changes in the vertebral column are common. Singh and Jolly (1961) give a full account of the clinical features of chronic fluorosis in North India where, in localised areas, the water may contain 14 p.p.m. of fluorine.

Nevertheless there is no evidence that fluorides in small amounts, such as occur regularly in human food and water, or in the concentrations recommended for the prevention of dental caries, have any deleterious effect (Chapter 54) and do not even cause mottling of the teeth.

Even a habitual intake of fluorine several times greater than normal appears to have no deleterious effect on health. An elaborate survey carried out in Texas showed that in one town (Bartlett) with an unusually high fluorine content in its drinking water (8 p.p.m.) the incidence of disease was no different from that in another town (Cameron) with a water content of 0·4 p.p.m. except that there was a slightly lower incidence of cardiovascular abnormalities in the former (Leone *et al.*, 1955). In the United Kingdom trials the organisers kept in constant touch with the 89 general practitioners and the public health authorities in the districts oncerned. There was at no time any evidence to suggest that the addition f fluorine to the drinking water increased the incidence of any disease or ndeed had any effect on the health of the people, *except for the benefit to he children's teeth.*

COMMENT.—There has been considerable opposition to fluoridation rom those who react emotionally to any suggestion of an enforced lteration in the natural quality of their food and drink. But it is surely easonable that people unfortunate enough to have a defective water supply hould sanction the efforts of public health experts to improve it to the evel enjoyed by others more fortunate. Those opposed to any alteration o the ' natural ' qualities of their sustenance will do well to read Chapter 24, where they may find alternative outlets for their crusading.

It is clearly essential that the modern city dweller should be provided with a supply of water that is safe, clean and pleasant to taste. In many localities it is inevitable that the water may need to be treated in various ways. Bacteria must be killed and bad-tasting organic material precipitated. If the water is too hard, it may be goitrogenic and should be softened. If it contains unnaturally small amounts of fluorine—insufficient to confer protection against dental decay—it seems reasonable that fluorine should be added to the extent necessary to bring its concentration to a satisfactory level.

CHAPTER 13

THE VITAMINS

DEFINITION

THE vitamins are organic substances which the body requires in small amounts for its metabolism, yet cannot make for itself at least in sufficient quantity. For the most part they are not related chemically and differ in their physiological actions.

HISTORY

The brilliant research of biochemists in the first half of this century led to the isolation of more than a dozen vitamins as pure chemical substances. The general procedure employed was first to study the effects of a deficient diet on a laboratory animal, and then to find a food that would prevent the deficiency. By a variety of chemical manipulations the particular nutrient concerned was gradually concentrated from the food, testing the potency at each stage of concentration on further batches of animals. This laborious procedure has been simplified in recent years by the discovery that several vitamins are also growth factors for micro-organisms which can therefore replace animals in testing for potency. By such methods it has been possible to isolate vitamins and subsequently to identify them chemically. The next remarkable achievement has been the direct synthesis by chemists of at least ten vitamins identified in this way.

Synthetic vitamins first became available for clinical trial in the 1930's and were in general use in the next decade. Books devoted to human nutrition gave them much space. However, time and experience have served to temper the initial enthusiasm for them. They have given no undisputed assistance to the practical problems of feeding people. Although of great value in treating certain nutritional disorders (Part III), they have proved of limited use in general medical practice.

NOMENCLATURE

When the early vitamins were discovered, each was labelled with a letter to distinguish it from those already known. But once a vitamin had been isolated and its chemical structure identified, it was given a specific name. It is entirely correct to use this specific name provided it is certain that a single pure chemical substance is referred to. However, there are advantages in certain circumstances for retaining some of the original letters as labels for the following reasons :

1. Not all of the vitamins are single pure chemical substances. Thus

itamins A, D, K, E, B_{12} and folic acid each consist of several closely elated compounds with similar physiological properties.

2. It is useful still to talk about the ' vitamin B complex ' because the itamins concerned in it (though unrelated chemically) often occur together n the same foodstuffs. The B complex was originally divided into ' heat-abile vitamin B_1 ' (now regarded as identical with thiamine) and heat-stable vitamin B_2 ' which is now known to consist of riboflavin, icotinic acid and other factors. This distinction between the heat-labile nd heat-stable fractions is no longer useful, particularly since antothenic acid is heat-labile and should therefore properly be regarded s part of vitamin B_1, though by custom this term is reserved exclusively or thiamine.

Factors Influencing the Utilisation of Vitamins

1. **Availability.**—Not all of the vitamin may be in absorbable form. For instance some of the nicotinic acid in maize is bound in such a way hat it is not absorbed from the gut. Fat-soluble vitamins may fail to be absorbed if the digestion of fat is impaired.

2. **Antivitamins.**—These are known to be present in some natural foods as further discussed in Chapter 25. Several synthetic analogues of vitamins have proved to be highly poisonous (*e.g.* aminopterin, desoxypyridoxine), presumably because they block the enzymes with which the true vitamins are concerned.

3. **Provitamins.**—Substances occur in foods which are not themselves vitamins but are capable of conversion into vitamins in the course of digestion. Thus the carotenes are the provitamin of vitamin A and, to some extent at least, the amino acid tryptophan can be converted to nicotinic acid.

4. **Biosynthesis in the gut.**—The normal bacterial flora of the gut is capable of synthesising significant amounts of certain vitamins (*e.g.* vitamin K, nicotinic acid, riboflavin, vitamin B_{12}, folic acid). Bacteria are also capable of extracting vitamins from the ingested food and retaining them until excreted in the fæces. In health the small intestine of man is for the most part sterile. The large intestine carries a heavy load of bacteria, but usually absorption from the large intestine is limited to water and salts. It is unlikely that bacterial activity significantly affects the amounts of vitamins available to a healthy human body. When intestinal disease is present, and particularly if there is diarrhœa (a common concomitant of nutritional disorders), the small intestine may harbour very large numbers of bacteria. These may significantly affect the amounts of available vitamins ; they are more likely to reduce than to increase the amounts as is clearly demonstrated in the blind loop syndrome.

The administration of poorly absorbed sulphonamides (*e.g.* sulphaguanidine) or antibiotics (*e.g.* tetracycline) can virtually sterilise the human gut of bacteria while allowing an overgrowth of yeasts. Changes in the mouth are produced which have been interpreted in the past as evidence of vitamin deficiency, though probably erroneously.

The administration of antibiotics to chicks and livestock can lead to marked increases in growth rates, perhaps by inhibiting bacteria that render dietary vitamins unavailable. But there is no evidence at present that the administration of antibiotics to man has any beneficial effect on growth or nutrition.

These considerations make clear how difficult it may be in practice to define the nutritive value of a diet in respect of a given vitamin by simple reference to a chemical analysis of its vitamin content.

Requirements

The true requirements for a given vitamin are likely to vary very much from one individual to another. Thus of three patients suffering from alcoholism—all apparently with similar histories—one may have scurvy, another beriberi and the third pellagra. It is impossible to state in advance the requirements of an individual for a particular vitamin in terms of the amount of the vitamin that should be present in his diet. Nevertheless it is useful to have some general guide as to whether his diet is likely to be adequate or deficient. For this purpose ' recommended allowances ' are given in the following pages.

Vitamins necessary for Man

It should be emphasised that the vitamins have been identified for the most part as nutrients necessary for various species of animals and bacteria. In this and the following chapter only those vitamins which have been proved (or been thought to be) necessary for man are considered.

Literature

A most readable and well illustrated introduction to the vitamins has been provided by Harris (1955). The postgraduate student and research worker will find the older literature on the vitamins usefully summarised in a three-volume monograph by Sebrell and Harris (1954).

FAT-SOLUBLE VITAMINS

VITAMIN A

History

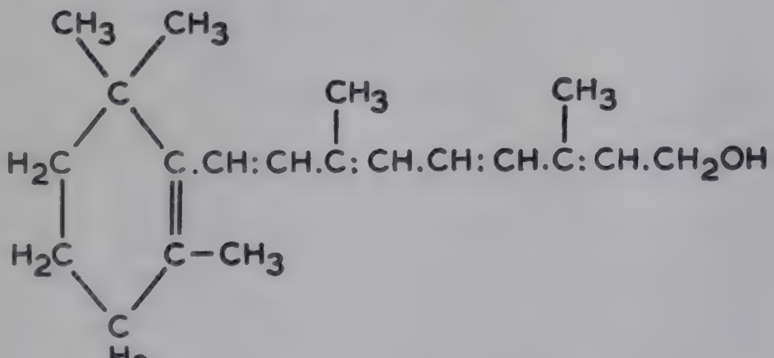
In a series of experiments carried out between the years 1906 and 1912 Sir Frederick Gowland Hopkins (1912) showed that young rats fed on a diet of casein, starch, sugar, lard and inorganic salts failed to grow and finally died. The addition to the diet of only 3 ml. of milk daily, supplying not more than 4 per cent. of the total calories, enabled the rats to thrive. He thus demonstrated the existence of an ' accessory food factor ' in milk. In 1913 two groups of American workers extracted this growth factor with ether, thus showing that it was fat-soluble. Osborne and Mendel (1913) extracted it from butter, and McCollum and Davis (1913) from butter, egg yolk and cod-liver oil. Two years later the latter workers proposed the name ' fat-soluble A ' to distinguish it from ' water-soluble B ' which they had detected in whey, yeast and rice polishings. Vitamin A, as it came to be called, was further distinguished from fat-soluble vitamin D following the demonstration that it was ineffective in the cure of rickets produced experimentally in puppies by Mellanby in 1918.

The relationship of vitamin A to the plant pigment carotene was first demonstrated by Rosenheim and Drummond (1920). They showed that the vitamin A potency of vegetable foods was closely related to their content of carotene—a pigment that had been isolated from carrots nearly a century before. The final proof that carotene is the precursor of vitamin A was largely due to the subsequent work of Moore (1957) at Cambridge, who has written an admirable monograph on the vitamin.

The chemical identification of vitamin A was achieved in the laboratories of Karrer in Switzerland and Heilbron in Great Britain between the years 1930 and 1932. Its final synthesis in 1947 is hidden in a confusion of commercial secrecy and competing patents.

CHEMISTRY

Vitamin A is found only in foods of animal origin. Animals obtain the vitamin from its precursor or ' provitamin '—the pigment β-carotene. A variety of chemically distinct carotenes are found in plant tissues, but β-carotene is the most important since it regularly occurs in association with chlorophyll, the green colouring matter of plants. The carotenes are responsible for much of the colour of red and yellow vegetables. The chemical structure of vitamin A is as follows :



vitamin A

The conversion of carotene into vitamin A in the human body is not complete and involves considerable losses (see below). It takes place largely, if not entirely, in the walls of the small intestine (Thompson *et al.*, 1949).

Another chemically distinct form of the vitamin—vitamin A_2—has been identified, but it is of no practical importance since it has been found only in the livers of freshwater fish.

Vitamin A itself is a pale yellow, almost colourless, compound, soluble in fats and fat solvents but not in water, stable to heat at ordinary cooking temperatures, but liable to oxidation and destruction when the fats that contain it turn rancid. Vitamin E, if present in the same preparation, will protect it from oxidation. Vitamin A is also destroyed by exposure to sunlight.

Units.—The international unit (i.u.) of vitamin A was introduced, before the final isolation of the vitamin, as a convenient index of its concentration in biological materials. One international unit is now known to be equivalent to 0·344 μg. of pure vitamin A acetate or 0·3 μg. of the vitamin. It is therefore possible to express the vitamin A content of a food in terms of μg./100 g., as with other vitamins of known composition. In practice, however, it is useful to retain the international unit in dietetic nomenclature, so that mixtures of vitamin A and carotene can be expressed in terms of *international units of vitamin A activity*. For a mixed diet, the following formula

$$\text{vitamin A activity} = \text{preformed vitamin A} + \frac{\text{total carotene values}}{3}$$

is a good approximation.

PHYSIOLOGICAL ACTION

It seems likely that vitamin A has a place in the metabolism of all human cells, but the precise way that it behaves is not yet explained in biochemical terms except in one situation—the retina of the eye. The ability of the eye to see in dim light is dependent on the presence of the retinal pigment *rhodopsin* (visual purple), which is bleached in the presence of light and in the process acts as a stimulus to the rods of the retina. The bleaching of visual purple is the means whereby the human eye can see at night. Vitamin A is an essential component of visual purple, so that patients suffering from vitamin A deficiency are often troubled with night blindness.

Elsewhere in the body the effects of vitamin A deficiency can be recognised only in terms of the morbid histology that it produces. Deficiency of this vitamin results in a morphological change, first described by Wolbach and Howe (1925), in the epithelial surfaces of all parts of the body except the gastrointestinal tract. Epithelial cells undergo *squamous metaplasia* whereby they become flattened and heaped one upon another. The sweat (sebaceous) glands of the skin and the tear glands of the eye become blocked with horny plugs of keratin so that their secretions diminish. The lack of tears and the heaping up of epithelium on the scleral conjunctiva produces the condition of *xerophthalmia*. If the cornea is affected, *keratomalacia* results. Plate III shows keratomalacia in a monkey after four and a half months on a diet deficient in vitamin A (Ramalingaswami *et al.*, 1955). In the skin the condition of *follicular keratosis* develops. In animals at least, similar changes occur in the epithelial lining of the bronchial tree, with loss of cilia, the accumulation of bacteria and fatal bronchopneumonia. Squamous metaplasia in the urinary tract of dogs results in the formation of urinary calculi, but there is no good evidence that vitamin A deficiency is a cause of renal stones in man. Lack of the vitamin in animals leads to irregular development of the skeleton, including the skull and vertebral column, with distortion and injury of the brain and spinal cord confined therein (Mellanby, 1950).

The structural defects that result in animals suffering from deficiency of vitamin A initiated hopes that superficially similar disorders in man might be cured by the vitamin, but these hopes have not been fulfilled.

Storage.—Healthy individuals in Britain may contain 300,000 to 500,000 i.u. in their livers (Moore, 1957). This is sufficient to meet requirements for many months or even a year with no dietary intake.

Human deficiency.—Vitamin A deficiency was induced in sixteen human volunteers in an experiment carried out in Sheffield from 1942 to 1944. Anyone with a special interest in vitamin A should certainly study the account (Hume & Krebs, 1949) of this investigation. It is noteworthy that although night blindness and some follicular keratosis resulted, there was no xerophthalmia. The clinical effects of vitamin A deficiency are usually seen only in people whose diet has been deficient for a long time both in dairy produce and fresh vegetables. In other words it is a disease of hot dry climates. Deficiency of vitamin A occasionally develops from faulty absorption, caused by a variety of diseases of the alimentary tract. Owing to the large stores of the vitamin this is very rare and could only occur in a previously healthy man after many months of severe illness.

Diagnosis.—The Sheffield experiment showed that the most sensitive test of vitamin A deficiency is the measurement of ability to see in dim light (' dark adaptation '). For this purpose Wald's method of measuring ' final rod threshold ' as modified by Dow and Steven (1941) is perhaps the most reliable.

Vitamin A can be measured in the blood by means of the blue colour that it develops in the presence of antimony trichloride (Carr-Price reaction). The level in the blood does not begin to fall until the body's reserves are severely depleted. The normal value of vitamin A in the plasma of apparently healthy individuals in Great Britain in 1952 lay between 50 and 300 i.u./100 ml. (mean 148). The level of carotenoids lay between 15 and 370 μg./100 ml., mean 133 (Leitner *et al.*, 1952). The average plasma level in the subjects of the Sheffield experiment was 90 i.u. at the start and fell only to 70 i.u. after a year on a diet virtually devoid of vitamin A and carotenes. On the other hand the level of ' carotenoids ' in the blood is influenced much more rapidly by recent changes in diet. In the Sheffield experiment this level started at 90 μg./100 ml. and fell to about 24 after two months on the diet and thereafter remained fairly stable. In a study in South India (Chandra *et al.*, 1960) the mean serum vitamin A was 80 i.u./100 ml. in apparently healthy children and 32 i.u./100 ml. in those with clinical features of vitamin A deficiency. Corresponding carotenoid levels were 50 and 18 μg./100 ml. The level of plasma carotenoids reflects the recent dietary intake of the precursor and gives no indication of the stores of vitamin A that may be present in the liver.

It should be emphasised that the carotenes are yellow pigments and when there are excessive amounts in the plasma they may be mistaken for bile pigments in the routine estimation of the icteric index. In diabetes mellitus, myxœdema and chronic alcoholism the plasma level of carotenes is sometimes elevated ; the skin, especially over the palms of the hands, and in the soles of the feet may become stained yellow with the pigment and this also occurs in the rare condition, idiopathic carotenæmia.

Dietary Sources

Preformed vitamin A is chiefly found in milk, butter, cheese, egg yolk, liver and some of the fatty fish. The liver oils of fish are the richest natural sources of vitamin A, but these are used as nutritional supplements rather than foods.

Carotene is widely distributed among plant foods. It is found chiefly in green vegetables in association with chlorophyll, so that the green outer leaves of vegetables like cabbage and lettuce are good sources of carotene, while the white inner leaves contain little or none. Other useful sources are yellow and red fruits and vegetables. All vegetable oils are devoid of vitamin A activity, with the exception of red palm oil which is extensively produced in West Africa, Indonesia and Brazil ; the cultivation of the oil palm is spreading slowly to other parts of the tropics. This oil is a rich source of carotene. In Great Britain and some other countries vitamin A is added artificially to margarine to provide the same concentration as that of good summer butter.

The yellow colour usually present in dairy products, cheese, butter and eggs, is due to carotene, but their colour gives no indication of the amount of colourless preformed vitamin A they contain.

Losses in the Preparation and Handling of Food

Both vitamin A and carotene are stable to ordinary cooking methods, though some loss may occur at temperatures above 100° C. as when butter or palm oil is used for frying. Fruits and other foods that are dried in the sun lose much of their vitamin A potency. The stability of carotene in tinned foods was dramatically shown by Drummond (1939) who found that cooked carrots that had been sealed in air-tight containers

TABLE 13, 1. *Sources of vitamin A and carotene*

Source	Description	Range (i.u./100 g. edible portion)
1. *Fatty fish and their oils*—		
Halibut-liver oil	...	2,000,000–36,000,000
Cod-liver oil	...	40,000–400,000
Cod-liver oil	B.P. (1953) standard	60,000
Cod-liver oil	British Welfare Foods (1958) standard	90,000
Shark-liver oil	...	45,000–600,000
Herring	Fresh	90
Salmon	Tinned	80–250
Sardine	Tinned	136–290
Tunny	Tinned	70–200
2. *Dairy produce*—		
Butter	...	2,400–4,000
Margarine	Vitaminised	2,000
Eggs	Fresh, whole	1,000–1,140
Milk	Fresh, whole	70–230
Cheese	Whole, fatty type	[illegible],200–1,740
3. *Meats*—		
Liver	Sheep and ox	4,000–45,000
Beef	...	0–50
Mutton	...	0–50
4. *Fruit and vegetables* *—		
Red palm oil	...	40,000–100,000
Carrots	...	10,000–20,000
Leafy vegetables †	...	80–12,000
Tomatoes	...	1,100–3,000
Apricots	Fresh	690–2,790
Bananas	...	100–300
Sweet potatoes	Colourless	500
Sweet potatoes	Red and yellow varieties	3,800–7,700
Orange juice	...	190–250
5. *Negligible sources*—		
Lard and vegetable oils	...	Trace only
Bacon and pork	...	Trace only
White fish	...	Trace only
Cereals (except maize)	...	Trace only
Sugar, jams and syrups	...	Trace only
Potatoes	...	Trace only

* Fruits and vegetables contain only the precursor carotene.

† Fully grown dark green leaves as commonly used in the tropics are in general a better source of vitamin A than hearts of lettuce, cabbage, etc.

in 1824 for the Arctic voyage of H.M.S. *Hecla* had much the same carotene content as fresh carrots when the containers were finally opened in 1939.

Considerable losses of vitamin A may occur in fish-liver oils bottled in colourless glass and displayed in shop windows before being sold to the public.

RECOMMENDED ALLOWANCES

Owing to the large stores in the liver, it is difficult to determine how much of the vitamin or its precursors should be taken from day to day in order to maintain this reserve. A further difficulty arises when a large part of the dietary needs are supplied by carotenes from vegetables, for the conversion of carotenes to vitamin A is always incomplete. The results of the Sheffield experiment indicated that only about one-quarter of the carotenes in carrots and other root vegetables is converted by the body into the vitamin. Less than half the carotenes in leafy vegetables undergo this conversion. On the whole it is a fair guess that about one-third of the carotenes in a mixed diet contributes to the vitamin A stores of the body. A satisfactory daily allowance in terms of vitamin A is 2500 i.u., or 7500 i.u. as carotene. The British Medical Association recommended 5000 i.u. as a satisfactory intake for an adult, having regard to the fact that in most diets the intake would be supplied in part by dairy produce and in part by vegetables. Recommended allowances for children and during pregnancy and lactation are given in Table 15, 1 and 15, 2, page 254.

Therapeutic Uses

Vitamin A is invaluable in the treatment of xerophthalmia and of night blindness—when this is due to dietary failure. It should also be given to malnourished people who show evidence of follicular keratosis. Cheap concentrated sources are halibut, cod, shark, tunny and swordfish liver oils. These are conveniently dispensed in the form of concentrated solution of vitamin A (B.P.) of which 0·6 ml. contains about 35,000 i.u. A total dosage of 250,000 i.u. given in capsules over a period of one week should achieve the maximum therapeutic benefit. Synthetic vitamin A acetate, though now available in pill form for therapeutic use, is more expensive and has no therapeutic advantage over halibut-liver oil.

In hot dry climates and elsewhere where vitamin A deficiency is endemic it is not always possible immediately to improve the food supply. The distribution of a natural concentrated source of the vitamin is then desirable, especially for the children. For this purpose cod-liver, shark-liver or red palm oil can usefully be given, according to which is most easily available locally. Two teaspoonfuls (about 8 ml.) of a B.P. preparation of cod-liver oil provides about 5000 i.u. of vitamin A, which is a satisfactory daily dose for prophylaxis. Other oils may be given in amounts containing equivalent quantities of the vitamin.

Where vitamin A deficiency is prevalent, it will often be found that minor disorders of the eyes and skin recover more rapidly in children receiving regular prophylactic doses of the vitamin. There is also the clinical impression that it often improves their growth and well-being.

The prescription of vitamin A for the prevention of the common cold and other infections in people taking a good mixed diet is not justified by any reliable clinical evidence.

Toxicity

Vitamin A is practically insoluble in water so that it is not excreted in the urine like the water-soluble vitamins when taken in excessive amounts.

It therefore accumulates in the body and can produce toxic effects. The early explorers of the Arctic learnt from the Eskimos that it is unwise to eat the liver of the polar bear; it causes drowsiness, headache, vomiting and extensive peeling of the skin. Analysis has shown that polar bear liver may contain nearly 2,000,000 i.u. vitamin A/100 g. approaching the concentration in halibut-liver oil (Rodahl & Moore, 1943). This may well account for its toxicity.

In recent years about twenty cases have been described in the U.S.A. of children under 3 years old with vitamin A poisoning. Usually they have been the victims of misguided maternal enthusiasm, receiving a daily dose between 100,000 and 500,000 i.u. for several months. Some concentrated preparation, such as halibut-liver oil, has usually been given in doses appropriate for cod-liver oil in the mistaken belief that if a little does good, a great deal more should do even better. The characteristic changes observed were anorexia, irritation, a dry itching skin, coarse, sparse hair and swellings over the long bones due to bony exostoses. The liver was sometimes enlarged. Examination of the blood showed the level of vitamin A in the plasma to be in the region of 300 i.u./100 ml. The serum alkaline phosphatase was increased. Rapid recovery followed withdrawal of the vitamin.

VITAMIN D

History

Cod-liver oil was used in Scotland as a traditional folk remedy at least as early as the eighteenth century. Its nutritional value was recognised by Professor Hughes Bennett (1812-75) of Edinburgh. The famous French physician, Trousseau, began to use it in the treatment of rickets about one hundred years ago. Sir Edward Mellanby (1918) first clearly showed by his classical studies on puppies that rickets is a nutritional disease responding to a fat-soluble vitamin present in cod-liver oil. Plate IV shows a rachitic dog brought up on a diet deficient in vitamin D (Mellanby, 1934). This vitamin was finally prepared in pure form in 1931 simultaneously in Great Britain and Germany.

Chemistry

A number of distinct but closely related compounds possess rickets-preventing (antirachitic) properties. These are all sterols, chemically related to cholesterol and to the hormones of the adrenal cortex and sex glands (Table 6, 1). Certain sterols on exposure to ultraviolet irradiation undergo a small structural change which makes them antirachitic. This change involves little alteration in their ordinary chemical properties. Only two 'activated' sterols are of importance in nutrition and therapeutics. These were first described as vitamin D_2 and D_3 and are still known by these labels. The material originally described as vitamin D_1 was subsequently shown to be an impure mixture of sterols.

Calciferol (Vitamin D_2).—Calciferol is manufactured by exposing ergosterol, a sterol found in fungi and yeasts, to the action of ultraviolet light. Irradiation of ergosterol gives rise to several related substances —some toxic—of which only calciferol has marked antirachitic properties. In the manufacture of calciferol the irradiation has to be carefully controlled so that toxic substances are not present, except in traces, in the final product.

Although calciferol is widely used in therapeutics, it occurs very rarely in nature. It is absent in almost all plant and animal tissues except for small amounts in certain fish-liver oils. Ergosterol, from which it is derived, occurs only in plants.

Vitamin D_3.—This substance is the natural form of vitamin D. It is produced by the ultraviolet irradiation of 7-dehydrocholesterol, a sterol widely distributed in animal fats, such as the oily secretions of mammalian skin and the oil of the preen glands of birds.

Physiology

Activation of 7-dehydrocholesterol takes place when the surface of the body is exposed to sunlight. In man the vitamin so formed enters the body directly by way of the skin. In other mammals and birds the entry is by ingestion through the gut, as a result of licking the fur or preening the feathers.

The liver oils of fish are very rich in vitamin D_3, probably from the ingestion of microscopic plankton that live near the surface of the sea and are hence exposed to the sun's rays.

Calciferol and vitamin D_3 are equally potent in protecting rats from rickets, but vitamin D_3 is considerably more potent for chickens. There is no indisputable evidence of a similar difference in potency in man.

Ingested vitamin D requires the presence of bile and probably fatty acids for its absorption in the gut. It is stored in the fatty tissues of the body. Any excess is probably eventually eliminated in the fæces, or perhaps by slow metabolic destruction.

The one clearly defined action of vitamin D in the body is that it promotes the absorption of calcium from the gut. But it can also have other actions, including a direct action on the bones. Current knowledge directed towards elucidating the precise mode of action of vitamin D in the body has been ably reviewed by Kodicek (1956). Considerable advances have lately been made by studying its action on bacteria. Kodicek suggests that the vitamin acts by altering the permeability of cell membranes.

Pathology

In order to understand the morbid anatomical changes that take place as a result of vitamin D deficiency, it is necessary first to consider the normal processes involved in the growth of bones.

Bone growth.—Growth in length of the long bones normally occurs at the and of epiphyseal cartilage lying between the shaft (or diaphysis) and the piphysis. New cartilage is continuously formed at the epiphyseal end, while t the diaphyseal end the cartilage degenerates and is invaded by capillaries and steoblasts, forming osteoid tissue in which calcium salts are deposited. The ormation of new cartilage keeps pace with its degeneration and with the imultaneous formation of new bone at the end of the diaphysis, so that the one grows in length. Growth ceases when no further new cartilage is formed nd the diaphyseal bone meets and fuses with the epiphysis.

Experiments on animals have shown that in vitamin D deficiency the epiphyseal cartilage grows, but the normal degeneration of this cartilage becomes defective, so that there is widening of the zone between diaphysis and epiphysis. At the diaphyseal end the cartilage is irregularly invaded by excessive osteoid tissue in which little calcification takes place. Calcification is also reduced beneath the periosteum which covers the outer surface of the bones ; there is an overgrowth of osteoid tissue below the periosteum and delay in the normal outward thickening.

These anatomical lesions in animals deprived of vitamin D are accompanied by the biochemical effects of calcium depletion and the general manifestations of rickets.

Vitamin D, by facilitating the absorption of calcium from the gut, ensures a sufficient supply of calcium in the extracellular fluids bathing the growing points of the bones. Here the calcium comes in contact with inorganic phosphates liberated from organic phosphates under enzymic influence. Thus calcium phosphate is formed and used by the osteoblasts to make new bone. The exact biophysical mechanisms involved are complicated and not, as yet, fully understood (Nicolaysen & Eeg-Larsen, 1953).

Sources

Table 13, 2 shows some useful sources of the natural vitamin. It will be seen that they are all fat-containing animal products. The international unit (i.u.) of vitamin D corresponds in antirachitic activity to 1 mg. of the international standard solution, which is equivalent to 0·025 μg. of crystalline vitamin D_3. The great variations in the values for any one source are no doubt due to differences in the diet—and the degree of exposure to sunlight—of the animal of origin.

Recommended Allowances

As already said, vitamin D is obtained by higher animals in two ways—by the action of ultraviolet light on the skin and by the ingestion of animal fats containing the vitamin. Because of these two diverse sources it is impossible to define dietary ' requirements ' in any precise terms. Only a few of the natural foods eaten by man contain vitamin D in significant amounts.

There is no evidence that adults need any dietary supply of the vitamin, TABLE 13, 2. *Natural sources of vitamin D*

Source	Range (i.u./100 g. edible portion)
1. *Fatty fish and their oils—*	
Cod-liver oil	8,000–30,000
Cod-liver oil, B.P. (1953) standard	>8,500
Cod-liver oil, British Welfare Foods (1958) standard	10,000
Halibut-liver oil	20,000–400,000
Swordfish-liver oil	1,000,000
Tunny-liver oil	85,000–25,000,000
Shark-liver oil	1,300–5,000
Fat fish (fresh or canned, *e.g.* herring, salmon, sardine, pilchard)	200–1,800
2. *Dairy produce—*	
Eggs (whole)	50–60
Eggs (yolk)	150–400
Margarine (vitaminised)	80–350
Butter	10–100
Cheese	12–15
Milk	1–4

Cereals, vegetables and fruit contain no vitamin D. Meat and white fish contribute insignificant amounts.

although a supplementary source is usually recommended during pregnancy for the benefit of the infant. Infants and young children, especially if their environmental circumstances predispose to rickets, require a supplement of vitamin D as discussed in Chapter 29.

PROPHYLACTIC AND THERAPEUTIC USES

In general, ordinary foods should not be relied upon to supplement satisfactorily the vitamin D derived from the skin. When supplements are needed, cod-liver oil is the best natural source for most purposes. Shark-liver oil is often available in the tropics, but usually contains less vitamin D than cod-liver oil.

Vitamin D is invaluable in the treatment and prevention of rickets and osteomalacia. It is also useful in correcting low levels of serum calcium such as occur in the malabsorption syndrome and hypoparathyroidism. It is the only vitamin that has undisputed uses as a drug in the treatment of disease unconnected with nutritional failure. Vitamin D revolutionised the treatment of *lupus vulgaris* (tuberculosis of the skin). Massive doses of vitamin D (*e.g.* 150,000 i.u. of calciferol daily by mouth) were often curative, though nowadays it has been largely supplanted by chemotherapeutic drugs. The success of calciferol therapy in lupus has led to its trial in other skin diseases with generally disappointing results.

Toxic Effects

The fat-soluble vitamins, in contrast to those that are water-soluble, re not rapidly excreted or metabolised and, if taken in excessive amounts, may accumulate in the body, producing undesirable toxic effects. Toxicity rom excessive calciferol may arise in at least two circumstances : when it s given in massive doses for the treatment of lupus or other diseases, and when the mother of an infant mistakes her instructions and gives some concentrated calciferol preparation by the teaspoonful—in the mistaken belief that it is similar to cod-liver oil—without realising that it may be fifty times more potent.

The earliest toxic symptom in children is usually sudden loss of appetite. Nausea and vomiting are frequently associated. Intense thirst and corresponding polyuria soon follow. Severe constipation may alternate with bouts of diarrhœa. Pains in the head and elsewhere are frequent but inconstant features. The child becomes thin, wan, irritable and depressed, gradually falling into a stuporose condition which may suggest meningitis. Fatal cases have been reported in which metastatic calcification was found at autopsy in the arteries, renal tubules, heart, lungs and elsewhere. It is possible that some of the earlier reported cases would now be described as suffering from idiopathic hypercalcæmia, a disease of infants which, as mentioned on page 166, has been thought by many pædiatricians to be due to overdosage with, or to a genetically induced hypersensitivity to, calciferol.

Changes in the blood give no certain guide to the severity of calciferol poisoning. The serum calcium may be elevated to 12 mg./100 ml. or even more, in which case the dose of the vitamin should certainly be reduced. It may remain normal. The serum inorganic phosphorus shows no regular change and the alkaline phosphatase is unaffected. The erythrocyte sedimentation rate is often increased, perhaps because of an increase in total serum proteins. Radiological examination of the bones shows an increase in density at the immediate growing points, but elsewhere the bones may be less well calcified than usual. Unless metastatic calcification is obvious, it requires a skilled radiologist to interpret the radiological appearances correctly. For the present the prevention and diagnosis of calciferol poisoning must rest with the clinician who detects the early symptoms and reduces the dose accordingly.

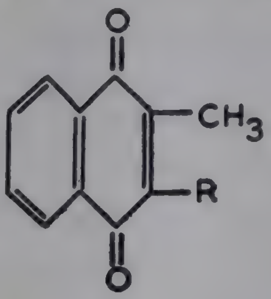
VITAMIN K AND RELATED SUBSTANCES

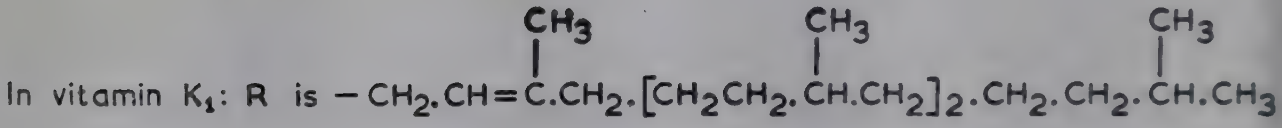
History

The Danish workers Dam and Schönheyder (1934) described a nutritional disease of chickens characterised by bleeding which was not due to vitamin C deficiency. Bleeding could be prevented by giving a variety of foodstuffs : lucerne (alfalfa) and decayed fish meal were particularly effective. The active principle in these materials could be extracted with ether and thus a new fat-soluble vitamin was discovered. Dam (1935) named it vitamin K (Koagulations-vitamin). With the aid of the Swiss chemist Karrer and his colleagues, Dam finally isolated the vitamin in 1939. In the same year, and only a few months later, the successful synthesis of vitamin K was announced from three different laboratories in the U.S.A.

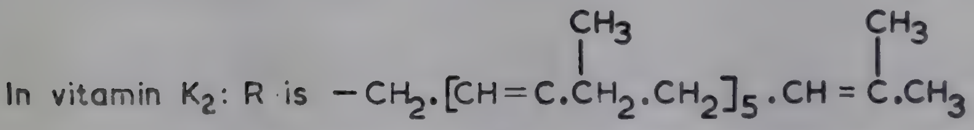
CHEMISTRY

The vitamin was found to exist in nature in two forms. Vitamin K_1 isolated from lucerne differs from K_2 from putrid fish meal in the nature of the side-chain, as shown in the following diagram :





In vitamin K_1: R is $-CH_2.CH{=}\overset{\overset{CH_3}{|}}{C}.CH_2.[CH_2CH_2.\overset{\overset{CH_3}{|}}{C}H.CH_2]_2.CH_2.CH_2.\overset{\overset{CH_3}{|}}{C}H.CH_3$



In vitamin K_2: R is $-CH_2.[CH{=}\overset{\overset{CH_3}{|}}{C}.CH_2.CH_2]_5.CH{=}\overset{\overset{CH_3}{|}}{C}.CH_3$

In menaphthone 2-methyl-1:4-naphthoquinone, R is H

Since vitamin K_2 is not important in medical practice it need not be discussed further.

Natural vitamin K_1 is a yellow oil, soluble in fat solvents, but only slightly in water. Synthetic vitamin K_1 (Konakion, Roche Products) is soluble in water and is to be preferred for therapeutic purposes. It can be given orally or parenterally. Analogues of naphthoquinone have been synthesised and most of them have been found to have vitamin K activity. Menaphthone is a yellow crystalline substance dissolving in fat solvents but only slightly in water. For this reason it has been replaced in medical practice by water-soluble analogues such as Synkavit (Roche Products) and Kapilon (Glaxo) which are inexpensive and effective in some hypoprothrombinæmic states (p. 207).

PHYSIOLOGICAL ACTIVITY

Vitamin K is necessary for normal formation of prothrombin in the liver. Prothrombin is a glycoprotein present in the blood plasma and necessary for the normal clotting of blood. In vitamin K deficiency the time that the blood takes to clot (the ' clotting time ') is prolonged. The amount of prothrombin in the blood can be roughly gauged by a special test which measures the clotting of plasma under standard conditions (the 'prothrombin time'). Prothrombin formation takes place in the liver; but the manner in which vitamin K participates in this process is not understood.

Bacterial synthesis.—Many species of bacteria synthesise vitamin K, though why they do so and what use they make of it is unknown. The putrefying action of bacteria in decayed fish meal first revealed the existence of the vitamin. The *E. coli* that inhabit the human large intestine synthesise it. It is often assumed that this biosynthesis in the gut provides for the needs of the body and explains why human beings (with the exception of newborn infants) appear to be independent of their diet for their supply of vitamin K. Nevertheless there have been some recent doubts about the physiological importance of substances produced by bacterial action in the alimentary tract. If the bacterial flora of the gut were the essential source of vitamin K in the body, it might be supposed that the prolonged administration of a bacteriostatic drug, such as sulphaguanidine, by depressing the growth of this flora would ultimately lead to a deficiency of vitamin K and a prolonged prothrombin time. Though this has been reported to occur in rats, there seems to be no clear evidence that sterilisation of the human gut by bacteriostatic or bactericidal agents has ever yet caused vitamin K deficiency in man.

HUMAN DEFICIENCY

Primary deficiencies

IN ADULTS this has never yet been clearly demonstrated, either by observation of malnourished patients or by dietetic experiments on volunteers. Hence it must be assumed that even the worst diets contain enough of the vitamin to satisfy normal human needs, or alternatively that the bacteria of the large bowel pay the price of their lodgings by contributing naphthoquinones and perhaps other vitamins to their host.

IN INFANTS.—The newborn baby has a sterile intestinal tract and furthermore is apt to be fed on foods relatively free from bacterial contamination. Breast milk and clean cow's milk are very poor sources of the vitamin. Infants in the first week of life have less prothrombin in their blood than normal adults and sometimes have a prolonged prothrombin time. There is usually spontaneous improvement within a few days. At one time bleeding in the newborn was often attributed to lack of vitamin K, but now it seems more likely that the cause of such bleeding usually lies in the liver, which is sometimes slow in starting the production of prothrombin and perhaps other factors concerned with clotting.

Conditioned deficiencies

Defects in absorption.—As vitamin K is fat-soluble, it is not surprising that any defect in the intestinal absorption of fats may result in conditioned vitamin K deficiency. This certainly occurs in two circumstances: (i) *Biliary obstruction*—A secretion of bile salts is as necessary for the normal ingestion of vitamin K as for other fat-soluble substances. Severe bleeding during or, more frequently, a day or two after an operation for the relief of jaundice due to obstruction of the common bile duct was a complication much feared by surgeons. To-day it is recognised that this danger can be circumvented by giving vitamin K by injection prior to the operation. (ii) *Malabsorption*—In sprue, idiopathic steatorrhœa, ulcerative colitis and other conditions in which fats are not effectively absorbed, bleeding due to deficiency of vitamin K may occur.

Defect in synthesis.—In severe disease of the liver the synthesis of prothrombin may fail and bleeding result, despite every effort of the physician to provide an ample supply of vitamin K.

Interference with the clotting of blood.—It has been known for some time that cattle develop a tendency to bleed if they are fed on spoilt sweet clover. The substance responsible for this effect was isolated and synthesised as dicoumarol by Stahmann, Huebner and Link (1941) in Wisconsin. Dicoumarol reduces the prothrombin time of the blood; this remarkable discovery has opened up a whole new field in the treatment of human diseases in which it is desirable to reduce blood coagulation, *i.e.* in arterial or venous thrombosis.

Dicoumarol itself has now been replaced in clinical use by other synthetic analogues such as tromexan and dindevan; the manner in which they affect the clotting of blood is still not fully understood, but interference with the synthesis of 'Factor VII,' and other components concerned in the clotting mechanism, is one of their main actions. Overdosage with these drugs can be overcome at least in part by adequate dosage with synthetic vitamin K_1 (p. 206).

Laboratory Diagnosis

The effects of vitamin K deficiency can be detected by determining the 'prothrombin time.' The essential basis of this test is as follows: freshly drawn blood that has been prevented from clotting by the addition of oxalate (which precipitates calcium) is centrifuged. To the separated plasma is then added an excess of calcium salts (to overcome the effect of the oxalate) and also a source of thromboplastin (generally derived from brain tissue). The time it then takes for the plasma to clot is taken as a measure of its prothrombin content. However, other factors in the plasma are probably also involved in this complex reaction.

Dietary Sources

Vitamin K is present in fresh dark-green vegetables, such as kale, spinach, nettles and lucerne. Cauliflower is a good source and also extract of pine needles. All foods of animal origin, including fish-liver oils, are

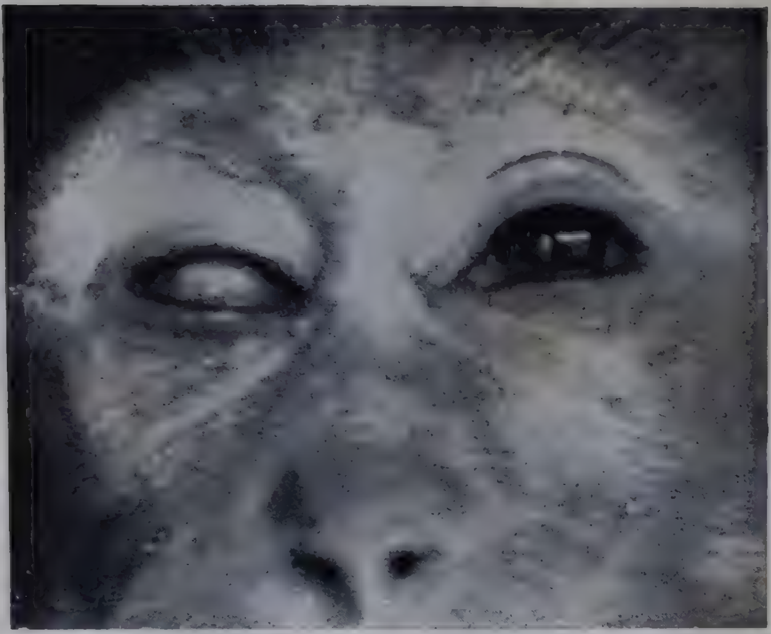


PLATE III. Keratomalacia of right eye in a monkey after 4½ months of a diet deficient in vitamin A. From the *Quarterly Journal of Experimental Physiology* (RAMALINGASWAMI *et al.*, 1955).

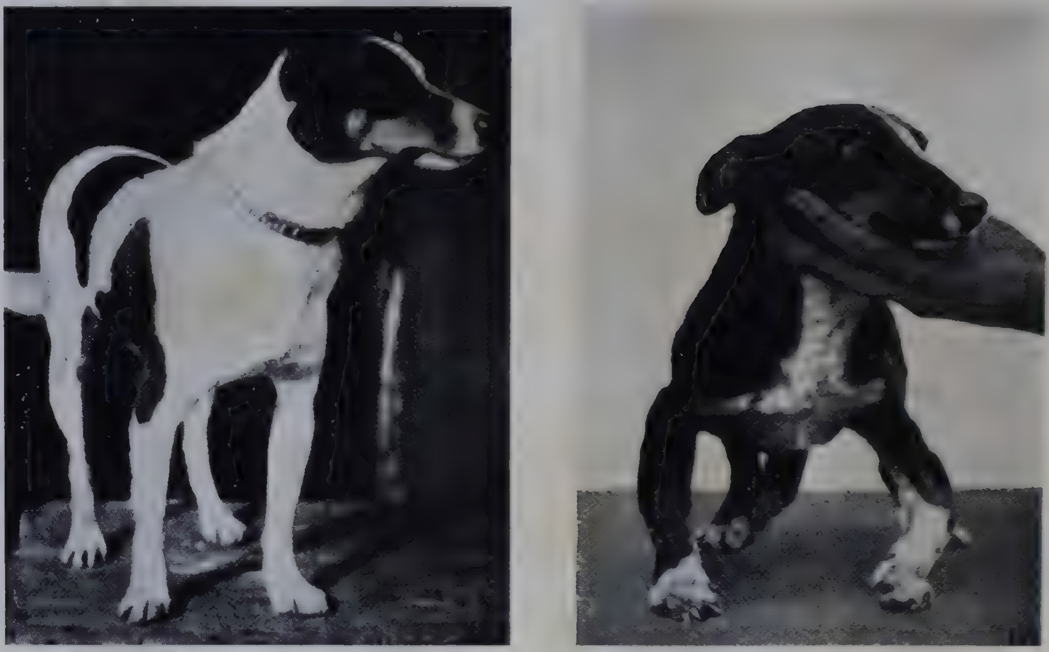

A B

Plate IV. A, A normal dog reared on a good diet rich in vitamin D (cod-liver oil) during a period of confinement. B, A rickety dog brought up on a diet similar to A except that it was deficient in the antirachitic vitamin D. (The cod-liver oil of A was replaced by olive oil.) By courtesy of Oliver & Boyd (Mellanby, 1934).

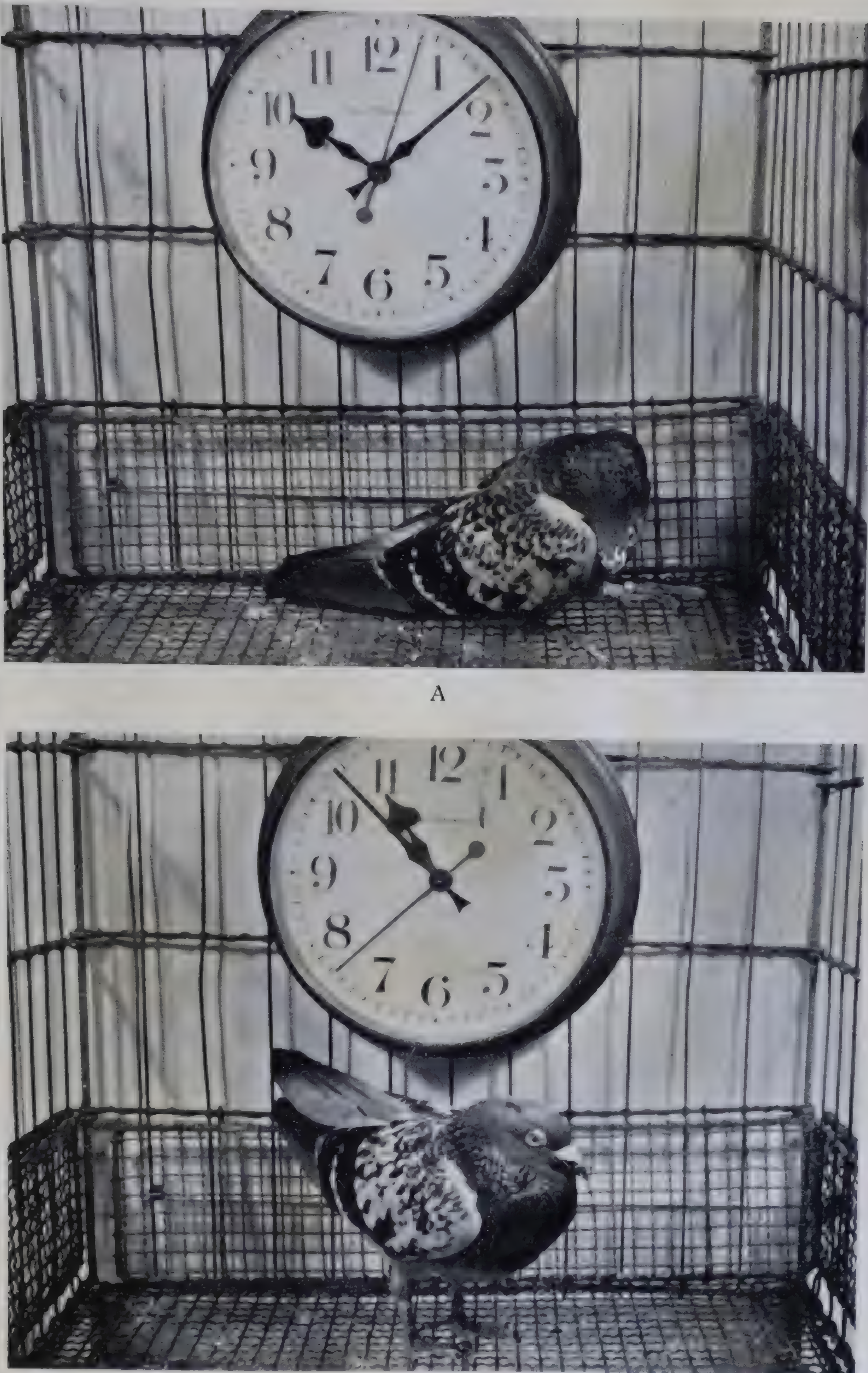
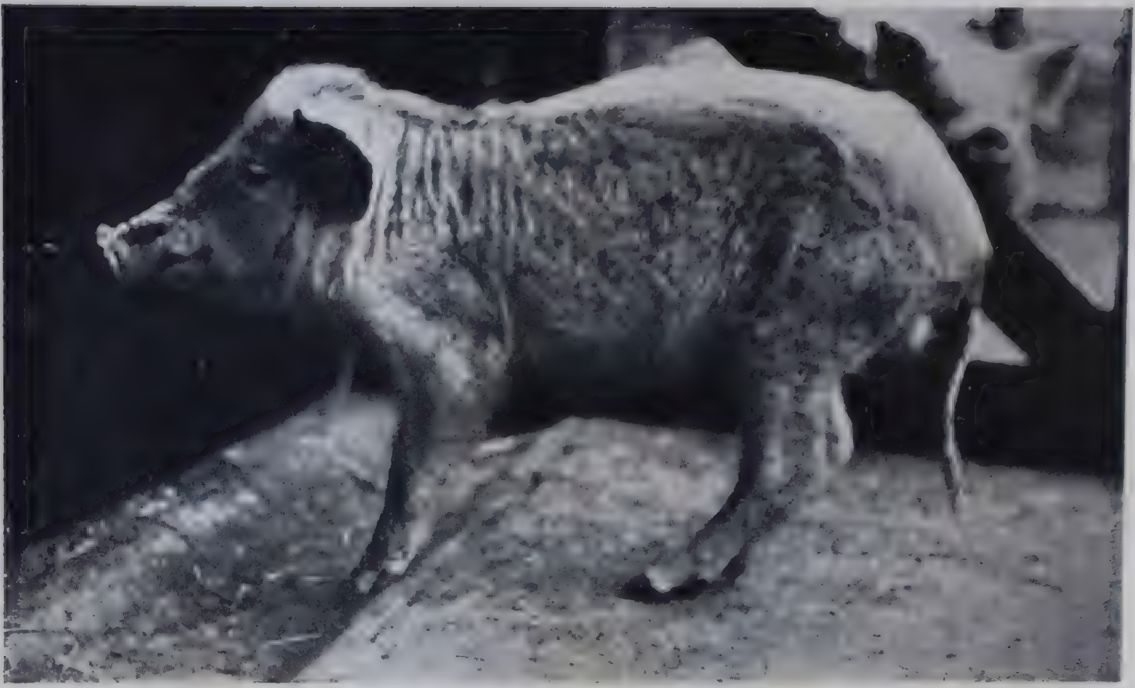
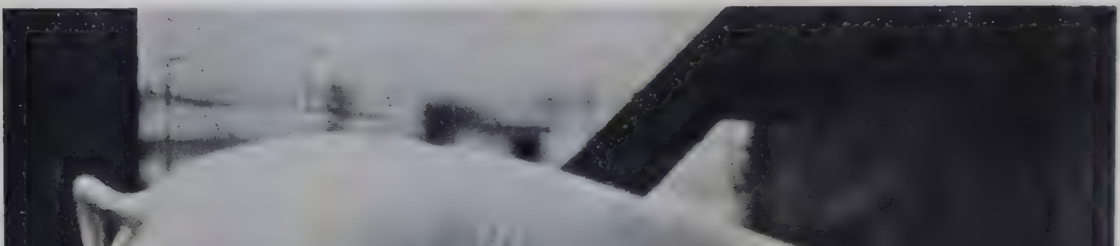


PLATE V. Cure of thiamine deficiency in a pigeon by intracerebral injection of thiamine

A, 10.08 A.M.—Continuous opisthotonos and rolling convulsions due to rice feeding. At 10.24 A.M. cerebral injection of 1·5 mg. thiamine-Cl(HCl) + 0·45 mg. glucose in 0·1 ml. saline was given. B, 10.52 A.M.—Showing degree of recovery as indicated by normal stance. From the *British Medical Bulletin* (PETERS, 1953).



A



B

PLATE VI. A, Pig, 6 months old, after 17 weeks on a maize + casein diet. Her weight was then only 36 lb. B, The same pig 3 months later; weight 129 lb. The diet had been the same in the interval except that 60 mg. of nicotinic acid had been added to her daily ration. From the *Biochemical Journal* (CHICK *et al.*, 1938).

To face page 209]

poor sources unless they have undergone extensive bacterial putrefaction. Inevitably there have been enthusiastic suggestions that we ought to eat more rotten food. Fortunately, however, there are no indications for prescribing a diet rich in vitamin K.

Therapeutic Uses

1. **In bleeding diseases of the newborn.**—In about 1 of every 300 infants born, bleeding occurs during the first four days of life somewhere in the body either into the skin, nervous system, peritoneal cavity or alimentary tract (melæna neonatorum). Vitamin K deficiency is not always the cause and trauma at birth may undoubtedly be responsible in some cases. Obstetric units no longer give vitamin K as a routine prophylactic measure, but confine its use to the prevention of bleeding in newborn infants who have suffered from trauma at birth or show signs of melæna neonatorum. In such cases small doses of a water-soluble vitamin K analogue are recommended, *e.g.* Synkavit, 1 mg. intramuscularly every eight hours until bleeding has ceased. Larger doses may cause hæmolysis and kernicterus in premature infants. A transfusion of blood should also be given if bleeding is severe.

2. **In biliary obstruction and fistula, and in malabsorption.**—The administration of vitamin K preparations is invaluable in cases where its absorption has been impaired by lack of bile salts, pancreatic secretion or other causes of digestive failure and is an essential pre-operative measure if surgery is contemplated in such cases. Water-soluble vitamin K analogues are as effective as synthetic vitamin K_1 and are to be preferred because they are cheaper and can be given in larger doses without untoward effects. Synkavit or Kapilon can be given subcutaneously or intramuscularly in a daily dose of 10 to 20 mg. The prothrombin level is usually restored to normal within a week. When there is severe damage to the liver little or no improvement in the prothrombin level of the blood can be expected unless a blood transfusion is given.

3. **In anticoagulant therapy.**—When patients are treated with tromexan, dindevan or similar drugs, the ‘ prothrombin time ’ of their blood may fall to the point where bleeding results. When this happens, synthetic vitamin K_1, which is much more effective than the vitamin K analogues, should be given. In severe cases 20 mg. of Konakion can be injected intravenously and repeated in four hours if the ‘ prothrombin time ’ has not returned to a safe level. In less severe cases the drug can be given by mouth (20 mg. every eight hours).

Toxicity

Excessive doses have been reported to cause hæmolysis and hæmoglobinuria in infants.

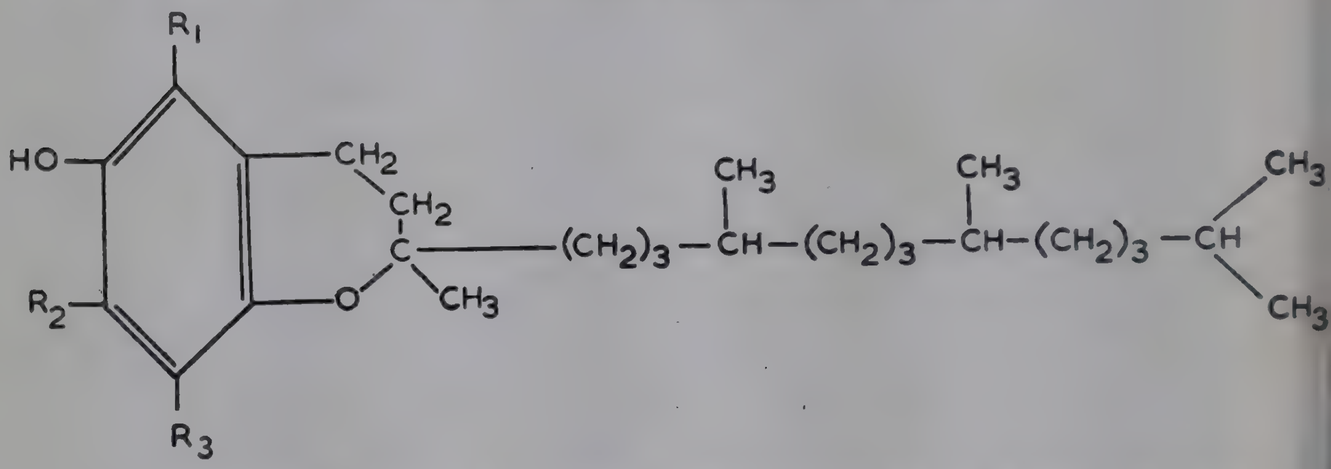
VITAMIN E (The Tocopherols)

History

Vitamin E was discovered by Evans and Bishop (1923) in California. They found that rats fed on a diet of casein, cornstarch, lard, butter and yeast fail to reproduce. Female rats aborted, while male rats became sterile. This could be corrected by the administration of certain vegetable oils. It was not until 1936 that Evans and his colleagues finally isolated pure vitamin E from the unsaponifiable fraction of wheat-germ oil. They called it tocopherol. The synthesis of α-tocopherol was accomplished in 1938 by Karrer and his colleagues in Switzerland and by Smith and his colleagues in the U.S.A.

Chemistry

Four different tocopherols have now been identified: α, β, γ and δ. They differ from each other in the position of the methyl groups round the ring of the molecule as shown in the following diagram:



In α-tocopherol R_1, R_2 and $R_3 = CH_3$; in β-tocopherol R_1 and $R_3 = CH_3$, $R_2 = H$; in γ-tocopherol R_2 and $R_3 = CH_3$ and $R_1 = H$.

All the tocopherols have the same physiological properties, although α-tocopherol—the form in which the vitamin is synthesised commercially—is somewhat more potent than the others. The tocopherols are yellow, oily liquids, freely soluble in fat solvents and remarkably stable to heat, even at temperatures above 100° C. In the presence of fats, however, they undergo slow oxidation and consequent inactivation. At the same time the fats are protected from oxidation by the tocopherols, so do not become rancid. Tocopherols protect both vitamin A and carotene from oxidation *in vitro*. This property puts them in the category of natural *antioxidants*.

It is still an advantage to retain the name vitamin E to mean any mixture of physiologically active tocopherols.

Physiological Action

The most interesting feature of vitamin E deficiency in rats is that they have a higher oxygen uptake than normal rats. In other words, the vitamin seems to act as an antioxidant not only *in vitro* but also *in vivo*. Biologists have long discussed the curious fact that although combustion takes place in the living matter it does not proceed with ever-increasing momentum as is usually the case when inanimate materials are ignited. Obviously there are controlling mechanisms that keep the fires of the body damped down to the appropriate level. At least one part of this mechanism appears to be the antioxidant activity of vitamin E. The excessive metabolic rate of vitamin E-deficient rats is due chiefly to increased metabolism in the muscles and as a result the muscles develop signs of wear and tear. The first sign is the appearance of creatine and pentose sugar in the urine, both of which substances are concerned with the release of energy in muscle. After a time the muscles become weak; they undergo fatty degeneration and fibrosis, reproducing the appearances seen in the muscular dystrophies of man.

Undoubtedly vitamin E deficiency affects other tissues besides the muscles; the death of the fœtus and the degeneration of the sperm-producing cells in the rat gave the first evidence of its existence. Thereafter a variety of additional abnormalities were described in rats and other animals deficient in the vitamin, though subsequent work often failed to reproduce the same effects.

Human Deficiency

So far there is no unequivocal proof that vitamin E deficiency ever occurs in man. The vitamin is certainly present in human tissues and there is good circumstantial evidence that it is necessary for their normal metabolism. But in view of its wide distribution in foods—even in the cheapest kind of poor cereal diet—it is most unlikely that dietary deficiency of the vitamin could arise. Gross or even lethal deficiencies of other nutrients would occur long before. It is possible that human tissues or the intestinal microflora are capable of providing for the needs of the body by direct synthesis of the vitamin.

There have been suggestions in the past that chronic deficiency of vitamin E may account for the falling birth-rate in certain countries, but this is a most improbable speculation. All public health experience shows that a falling birth-rate is associated with a high standard of living and a good mixed diet, whereas it is unfortunately true that people who live a marginal existence on the fringes of nutritional survival reproduce readily.

Dietary Sources

The tocopherols have been found in virtually every foodstuff used by man. The richest sources are fats of vegetable origin, particularly those derived from the germ of cereal grains, *e.g.* wheat-germ oil. Eggs are a good source. By contrast, animal fats and meats, fruit and vegetables are relatively poor. It has been estimated that a good, well-balanced Western type of diet provides about 20 mg. of mixed tocopherols daily.

Therapeutic Uses

Vitamin E is one of those embarrassing vitamins that have been identified, isolated and synthesised by physiologists and biochemists and then handed to the medical profession with the suggestion that a use should be found for it, without any satisfactory evidence to show that human beings are ever deficient of it or even that it is a necessary nutrient for man. There have been widespread empirical trials of α-tocopherol in an extraordinary number of human ailments. The initial reports of such trials have often erred on the side of optimism, particularly when there was no simultaneous study of control patients treated with dummy tablets of similar appearance. Thus although vitamin E has been recommended in the treatment of such diverse conditions as habitual abortion, sterility, muscular dystrophies, diabetes, ischæmic heart disease and skin disorders, there remains no satisfactory evidence that it is useful in any human ailment.

Toxicity

So far there is no evidence that the vitamin is poisonous, even in doses much above physiological levels. This is in marked contrast with other fat-soluble vitamins.

Chapter 14

WATER-SOLUBLE VITAMINS

ASCORBIC ACID—VITAMIN C

History

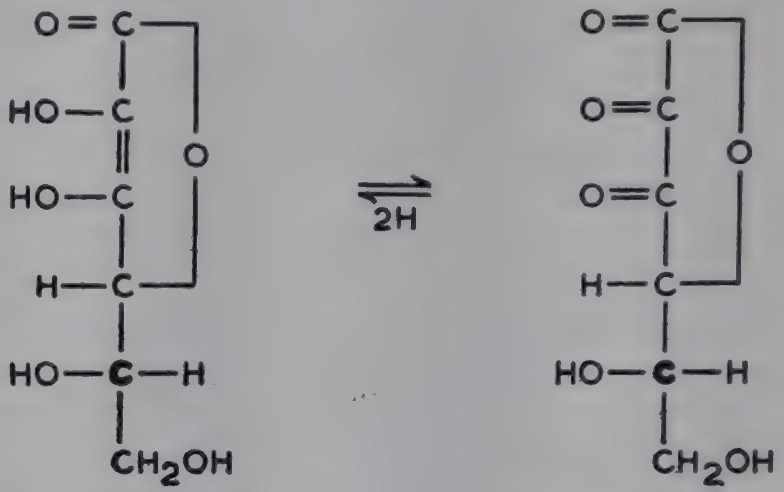
JAMES LIND (1753) remarked in his monograph on scurvy that the antiscorbutic effects of citrus fruits had been known for at least two hundred years before his time. He himself proved their value by means of a planned clinical experiment (Chapter 31). His teaching was put to practical effect by his pupil Sir Gilbert Blane, who first introduced a regular ration of citrus juice on ships of the Royal Navy, thus abolishing the scurvy that had hitherto been the scourge of ships' crews, and earning for British sailors the nickname ' limeys.'

With the rise of bacteriology in the nineteenth century, medical thought became dominated by positive agents in disease—bacteria or toxins elaborated by them. The idea of *deficiency diseases* was so neglected that in 1912 a naval officer, Captain Scott, R.N., ignoring the experience of the Royal Navy in the eighteenth century, planned an expedition to the South Pole without a single source of ascorbic acid in his rations. The story of that expedition is now tragic history. In the same year Sir Frederick Gowland Hopkins gave the first clear proof of the existence of the vitamins.

The first important step towards the final isolation of the antiscorbutic vitamin was the discovery by Holst and Frölich in 1907 that guinea-pigs, like man and monkeys, are susceptible to scurvy. Thereafter the search for the vitamin was directed towards isolating from citrus juices the pure chemical substance that would cure scorbutic guinea-pigs. But—as in the case of nicotinic acid (p. 228)—the first isolation of the vitamin came from an apparently unrelated field of biochemistry, that of tissue oxidation. Szent-Györgyi had been interested in the nature of substances with reducing properties in biological materials. In 1928, while working in Hopkins' laboratory, he isolated ascorbic acid from suprarenal glands, oranges and cabbage, though without recognising its properties as a vitamin. Thereafter, in 1932, another of Hopkins' students, C. Glen King, with his colleague W. A. Waugh, isolated the vitamin from lemon juice and identified it with Szent-Györgyi's acid. Within a few months Sir Norman Haworth, with his assistant E. L. Hirst (now Professor of Organic Chemistry at Edinburgh University), elucidated the chemical structure of ascorbic acid and accomplished its synthesis.

Chemistry

Ascorbic acid (AA) is a simple sugar. It is the most active reducing agent known to occur naturally in living tissues, and is easily and reversibly oxidised to dehydroascorbic acid (DHA). Their structural formulæ are :—



L ascorbic acid L dehydroascorbic acid

Ascorbic acid is a white crystalline substance, stable, when dry, in air and light. It is very soluble in water and then easily oxidised, especially in an alkaline medium and on exposure to heat, light and traces of metals, particularly copper. It is fairly stable in cold, acid solution. Though the first stage in its oxidation to DHA is reversible, further oxidation to diketogluconic acid cannot be reversed.

Effects of Deficiency on Tissues

Although the precise influence of ascorbic acid on tissue metabolism is not fully understood in chemical terms, the effects of its deficiency on the microscopic structure of tissues are well defined, chiefly through the work of Wolbach of Harvard, who from 1923 onwards made an intensive study of the tissues in scorbutic guinea-pigs (Wolbach, 1953). Ascorbic acid is necessary for the proper formation of the intercellular ground substance or matrix that binds together the cells in such mesodermal tissues as capillaries, bone, teeth and connective tissue. The cells of connective tissue —fibroblasts—normally lie in a bed composed of fibrils, strands and bundles of a protein, collagen. Collagen is formed by jellation of colloid protein in the matrix : ascorbic acid is evidently necessary for this process since the formation of new collagen ceases in scorbutic guinea-pigs ; the collagen gradually disappears and the supporting structure of the connective tissue collapses. Similarly in the bones and teeth, the lack of osteoid tissue and dentine in which calcium salts are normally deposited, prevents their further development. The teeth become loose through insufficient cement substance to bind them to the jaws. Lack of intercellular cement substance in the walls of the capillaries leads to their rupture and the production of petechial hæmorrhages.

PHYSIOLOGICAL ACTION

Ever since ascorbic acid was first identified and isolated as a reducing agent in living tissues, attempts have been made to ascribe to it a function in tissue oxidation, though so far without much success. Certainly the reduced form of the vitamin (DHA) can act as a hydrogen acceptor in the oxidation of the phenolic amino acids, phenylalanine and tyrosine ; but since only a small fraction of the vitamin is present as DHA in the body, it is very doubtful if this is its chief activity.

The normal human body when fully saturated contains about 5 g. of the vitamin, of which perhaps 30 mg. are in the adrenal glands, 200 mg. in the extracellular fluids and the rest distributed in varying concentrations throughout the cells of the body. The greatest concentration is in glandular tissues : the adrenal cortex (from which it was first isolated), pituitary gland, corpus luteum, pancreas, liver and spleen. Probably the most likely clue to the part that ascorbic acid plays in the metabolism of these active tissues will be found in the further study of the mechanisms which maintain the vitamin in the reduced state in living cells, despite the many oxidising agents they contain. Hopkins himself discovered that ascorbic acid could be protected from oxidation by glutathione (p. 130). The delicate balance between oxidised (DHA) and reduced ascorbic acid (AA) and oxidised (S-S) and reduced (SH) sulphydril may well be a factor in normal cell metabolism.

A curious feature of the metabolism of ascorbic acid, possibly related to its fundamental mode of action in the cells, is that any damage to the body such as a burn, fracture or surgical operation leads to a rapid disappearance of the reduced vitamin (AA) from the body ; its excretion in the urine ceases and there is a fall in the amount circulating in the blood.

The adrenal cortex

The first indication that ascorbic acid has a particular association with the adrenal glands was the observation of Sir Robert McCarrison (1919) that these glands are hypertrophied in scorbutic guinea-pigs. Van Eekelen and Kooy (1933) showed that fatigue in rats depletes the adrenal glands of ascorbic acid. Harris *et al.* (1937) produced the same effect by the injection of diphtheria toxin. Such noxious agents are now known to result in a discharge of adrenocorticotrophic hormone (ACTH) from the pituitary gland. Long (1947) showed that injected ACTH led to a rapid fall in the concentration of ascorbic acid in the adrenal glands which was followed by a reduction in their content of cholesterol and by evidence of secretion of the cortical hormones. The cholesterol that disappears is presumably the raw material from which the hormones are synthesised ; the disappearance of ascorbic acid which precedes it was at first interpreted as evidence that ascorbic acid assists in this synthesis. Now it seems much more probable that the ascorbic acid actually retards the formation of cortical hormones and must first be removed under the influence of ACTH before their synthesis can proceed (Meiklejohn, 1953).

The apparent association of ascorbic acid with the hormones of the adrenal cortex is of the greatest interest because both are intimately concerned with the integrity of connective tissue. The discovery in 1948 of the effects of cortisone in rheumatoid arthritis and other diseases affecting connective tissue was a dramatic event in the history of medicine. Here are two materials—ascorbic acid and the cortical hormones—both of which have an influence on the mesodermal matrix and both are concentrated in the same gland. It is logical to assume that their mode of action is in some way related. Indeed it has even been suggested that the whole effect of ascorbic acid on connective tissue is mediated through the adrenal cortical hormones. However, there is a great deal of evidence against this view. For instance patients whose adrenal glands have been removed or destroyed, suffer from Addison's disease but do not develop scurvy ; patients with an overactive adrenal cortex have Cushing's disease in which no abnormality of ascorbic acid metabolism has yet been demonstrated (Kark, 1953). Cortisone has no effect on the scorbutic lesion in guinea-pigs (Wolbach & Maddock, 1952). It must be remembered that by far the greater part of the ascorbic acid content of the body lies within cells elsewhere in the body ; the amount in the adrenals at any one time is a very small fraction of the whole. There is no biological parallel to support the hypothesis that all the other cells are simply holding the vitamin as a static reservoir, waiting for the adrenals to find a use for it. The vitamin, with its strong reducing properties, is no chemically inert substance like fat, that can easily be stored. It seems much more likely that it is intimately and actively concerned with the physicochemical activity of every cell that contains it.

The disappearance of ascorbic acid from the blood and urine following injury is not apparently due to the action of ACTH which is discharged from the pituitary under such circumstances, since so far as is known ACTH affects only its target cells in the adrenal cortex. What happens to the ascorbic acid that disappears ? Some may be diverted to the site of the injury and be retained or catabolised there. But this seems scarcely sufficient to account for the large amounts that sometimes vanish. Perhaps other tissues elsewhere in the body destroy the vitamin in response to some unknown hormonal influence similar to that of ACTH on the adrenal cortex, but more general in its effects.

The disappearance of ascorbic acid that occurs as a result of injury must be remembered in the dietetic treatment of convalescent patients.

Experimental Deficiency in Man

Observations on the nutrition of animals have contributed much to modern knowledge of human nutritional needs, but have left unanswered some questions that can only be solved by direct experiment on human olunteers. Although the guinea-pig enabled ascorbic acid to be iscovered, it could not provide information on human needs for the itamin.

The first man to attempt to induce scurvy in himself was an Edinburgh-trained physician, William Stark. He was encouraged thereto by the stimulating conversation of Benjamin Franklin. He died in the attempt in 1770 (Drummond & Wilbraham, 1935). This dangerous experiment was not undertaken again until 1940 when a young American surgeon, John Crandon, fed himself for six months on a diet practically devoid of ascorbic acid (Crandon *et al.*, 1940). This experiment was repeated in 1944-45 on twenty volunteers in Sheffield (Bartley *et al.*, 1953). Much of the information contained in the following sections is derived from these two admirably conducted experiments.

Blood Formation

Anæmia is a common but inconstant feature of human scurvy (Mettier *et al.*, 1930 ; Bronte-Stewart, 1953). In a large group of adult cases one may expect to find about one-third with 2 to 3 million red blood corpuscles/mm.^{3}, one-third with 3 to 4 million and the remaining third showing slight or no anæmia. The fact that patients with scurvy are sometimes anæmic has long suggested that ascorbic acid is concerned with the formation of red blood corpuscles—with erythropoiesis. Yet in the two experiments already mentioned, in which ascorbic acid deficiency was studied in human subjects with optimum quantities of other nutrients in the basic diet, no anæmia developed. Crandon had more than 6 *l.* of blood withdrawn by venepuncture for various tests in the course of 6 months on the deficient diet ; but he did not become anæmic until towards the end, when he began to bleed. Quite obviously there is an important difference in this respect between experimental ascorbic acid deficiency and clinical scurvy as it is seen in hospital practice. Patients with scurvy have usually subsisted for long periods on diets that are seriously deficient in many other nutrients besides ascorbic acid. Goldberg (1961) has shown that if red blood cells from a healthy person, isotopically labelled, are injected into patients with scurvy they have a greatly diminished life. Red cells from scorbutic patients, if injected into healthy persons, survive normally. These results suggest that a hæmolytic state develops in scurvy and is responsible for the anæmia.

Wound Healing

The successful healing of a wound requires the formation of strong connective tissue in the scar. It has already been said that ascorbic acid deficiency results in a failure of collagen formation in connective tissue. It is scarcely surprising therefore that a feature of scurvy, both in man and guinea-pigs, is that wounds fail to heal. The scars of previous wounds may break down and become open sores again. The account (Walter,

1748) of Lord Anson's voyage round the world gives a graphic description of this.

> " But a most extraordinary circumstance, and what would be scarcely credible upon any single evidence, is that the scars of wounds which had been for many years healed were forced open again by this virulent distemper. Of this there was a remarkable instance in one of the invalids on board the *Centurion*, who had been wounded about fifty years before at the battle of the Boyne, for though he was cured soon after, and had continued well for a great number of years past, yet on his being attacked by the scurvy, his wounds, in the progress of his disease, broke out afresh and appeared as if they had never been healed : nay, what is still more astonishing, the callus of a broken bone, which had been compleatly formed for a long time, was found to be hereby dissolved, and the fracture seemed as if it had never been consolidated."

Opinions differ as to the degree of ascorbic acid depletion necessary to affect wound healing. After 3 months of deficiency a skin incision made on Crandon healed normally ; only after 6 months on the grossly deficient diet did a second incision completely fail to heal. Most British surgeons would probably agree that the state of ascorbic acid nutrition encountered in Great Britain is sufficient to ensure good scar formation after operations.

Blood Levels

When the human body is fully saturated with ascorbic acid the blood contains 1·0 to 1·4 mg./100 ml. Almost all of this is present in the plasma and in the reduced form (AA). In experimental human ascorbic acid deficiency the level in the blood falls to near zero after about a month on the deficient diet, yet definite clinical signs of deficiency do not appear for a further five months. It is evident, therefore, that ascorbic acid in the blood must fall to very low levels for many weeks before any harm develops. Blood values of 0·1 to 0·3 mg./100 ml. are commonly found in healthy people in Great Britain ; the level tends to have a seasonal variation, falling in the spring when fruit and vegetables are scarce and expensive and in particular when the ascorbic acid content of potatoes diminishes. Such low values are of little significance, since they give no indication of the amount of the vitamin available to the cells of the body. Fortunately there is one kind of active cell whose content of ascorbic acid can be measured without excising a piece of tissue for analysis, namely the white blood corpuscles. These can be separated from blood by centrifuging in a special dumb-bell-shaped tube. With excess of dietary vitamin they contain 20 to 40 mg./100 g. In the Crandon and Sheffield experiments the level did not reach zero until four months after the onset of dietary restriction.

Laboratory diagnosis

Saturation tests have been used for measuring the level of reserves in the body ; ascorbic acid is given by mouth and the dose required before an excess of the vitamin appears in the urine is determined. Unfortunately, however, the experience of the Sheffield experiment shows that saturation tests are unreliable in differentiating between individuals who have clinical evidence of deficiency and others whose intake of the vitamin has been very low but nevertheless sufficient to maintain apparent health (Krebs, 1953). Since it is precisely for those people whose intake has been small—on the borderline of deficiency—that a satisfactory test is needed, saturation tests must be regarded as unsuitable for clinical use, though sometimes helpful in connection with dietary surveys. For clinical purposes the estimation of the vitamin in whole blood or plasma gives the best general guide.

Natural Sources

Ascorbic acid has a more limited distribution than the other important water-soluble vitamins. Citrus fruits, currants, berries and fully grown green vegetables are the richest sources. Root vegetables and potatoes contain smaller amounts, but the latter, although containing a relatively low concentration, is nevertheless an important source. Potatoes, because of the amount normally eaten every day, account for a considerable proportion of the total ascorbic acid intake of the population of Great Britain and other European countries, especially among the poor who cannot afford to buy much fruit. Potatoes were particularly important during the second world war, when the supply of imported citrus fruits virtually ceased. Foodstuffs of animal origin contain only small amounts of ascorbic acid. The best of such sources are liver and other glandular tissues, *e.g.* the roe of fishes. But these animal sources cannot be considered as negligible, since they give protection to such people as the Eskimoes, whose diet often consists of little else than meat and fish. Although dried cereals and pulses contain no ascorbic acid, they all form the vitamin on germination. Sprouting pulses are a valuable antiscorbutic of proven value as discussed in Chapter 53.

Table 14, 1 gives values for the ascorbic acid content of some foods and natural antiscorbutic remedies.

Effects of Cooking and Processing Foods

Ascorbic acid is very easily oxidised and this process, if continued beyond the stage of dehydroascorbic acid, is irreversible, so that the vitamin loses its activity.

Many plants contain an enzyme—an oxidase—that facilitates the oxidation of the vitamin in the presence of air. This enzyme appears to have no direct contact with ascorbic acid in the intact plant ; but it is released from plant cells when leaves or fruits are damaged by drying, bruising, pounding or cutting with a blunt knife ; it then begins to destroy the vitamin. Like all enzymes, ascorbic acid oxidase is rapidly inactivated by heat. But heat facilitates the oxidation of the vitamin even in the absence of this enzyme, especially in a well-oxygenated, alkaline medium

TABLE 14, 1. *Sources of ascorbic acid*

Food	Description	Range (mg. ascorbic acid/100 g. edible portion)
Black currants	Fresh	90–300
Black-currant syrup	...	60
Rose hips	Fresh	70–460
Rose-hip syrup	...	150–200
Citrus fruit	Fresh or juice	25–60
Stone fruits	Apples, pears, plums	5–10
Soft fruits	Strawberries, raspberries, etc.	25–60
Bananas	...	10–30
Pineapple	...	30–60
Guava	...	10–400
Mango	...	10–50
Melon	...	1–45
Papaya	...	30–120
Canned fruit *	Various	1–25
Green leafy vegetables	Tropical, raw	50–220
Green leafy vegetables	Temperate, raw	10–60
Potato	Raw	10–30
Potato	Chips	10–30
Potato	Boiled	5–15
Sweet potato	...	20–30
Roots and pulses	Fresh	10–30
Tomato	Fresh or juice	20–25
Milk	...	0–1
Eggs	...	Trace
Fresh meat	...	Trace

* In general, losses of ascorbic acid during canning of fruit and vegetables may vary from 50 to 60 per cent. while ordinary cooking will cause losses of 50 to 75 per cent.

(*e.g.* one containing baking soda) and in the presence of traces of copper. Ascorbic acid is also very soluble in water, so that much of it may be lost when vegetables are cooked in more water than is necessary and the water then thrown away. Obviously *some* loss of ascorbic acid in cooking is inevitable (hence the value of fruits and vegetables that can be eaten in the raw state) but the loss can be minimised by choosing cooking methods which will avoid these various causes of destruction. The practical side of this is further discussed in Chapter 22.

RECOMMENDED ALLOWANCES

The problem of deciding how much ascorbic acid an individual should need is beset with difficulties. There are two schools of thought on the question. First, there are those who believe that ideally a man ought to be fully saturated with the vitamin so that every cell in his body contains as much as it can hold. Secondly, there are others who maintain that so long as he feels and looks well and any small injury heals normally, he is probably getting all the ascorbic acid he requires, even though his intake of the vitamin may be small, his tissues unsaturated and his blood almost devoid of ascorbic acid. The chief proponents of the first view are laboratory workers who argue from their experience with guinea-pigs. There can be no doubt that a guinea-pig to be in full health by every standard requires a very large intake of the vitamin, sufficient to maintain the body in a state of full saturation. The arguments of this school are supported by recent evidence that any unexpected injury may create unusual demands for the vitamin. It may therefore seem reasonable to ensure that the healthy body is protected against such eventualities. The opposing view (to which we subscribe) is that man differs from the guinea-pig in several respects. In the first place, a guinea-pig needs between 5 and 10 mg./day of ascorbic acid to keep in health, which is enough to cure a patient with scurvy, despite his much greater size. It is evident that the guinea-pig is peculiar in its needs for the vitamin and that in this respect at least, man may resemble other mammals more closely, such as the rat and pig, who need no ascorbic acid in their diet ; they appear to be able to make all they need in their own tissues. It is even possible that man can do the same to a limited extent.

The chief argument against the desirability of full saturation is that few people in Great Britain ever achieve it. It would need a revolution in British habits to eat fruit and vegetables up to a level comparable to that needed by the guinea-pig. In addition, there is the further theoretical question as to whether individuals, accustomed over a long period to a large intake of the vitamin, would be capable of adjusting their metabolism to any sudden and unexpected reduction in the supply. The fact is that the amount of the vitamin that the body uses up each day seems to depend on the intake to which it is accustomed. Thus an individual fully saturated on an intake of about 100 mg./day seems to use up this amount ; no large excess is excreted in the urine until even more is provided. Yet other individuals can keep fit on as little as 10 mg./day for many months, as was shown by the Sheffield experiment. It is evident that the amount of the vitamin that an individual uses each day cannot be taken as an index of his true requirement.

In the face of these difficulties the sensible policy is to recommend allowances based on the practical experience of the average level of intake on which populations have been known to keep fit, such as the population of Great Britain in the second world war, and to allow a sufficient margin of safety above the levels of intake that are known to be potentially scorbutic.

The League of Nations Technical Commission on Nutrition (1938) originally proposed that 30 mg./day was a suitable allowance for a normal adult. This recommendation received support from the results of the Sheffield experiment (Bartley *et al.*, 1953). The Committee on Nutrition of the British Medical Association in 1950 recommended 20 mg. for an adult, 30 mg. for adolescents and 50 mg. during lactation (p. 254). Such allowances are certainly not enough to maintain the body in a state of full saturation with the vitamin. The Food and Nutrition Board of the

United States National Research Council, believing this state to be desirable, recommended in 1943 that an adult should receive the much larger amount of 75 mg./day (p. 254). The Food and Nutrition Board still maintains this view, although most British authorities believe that this amount is excessive and unnecessary. In our opinion the recommendations of the B.M.A. are reasonable and practical.

Therapeutic Uses

Ascorbic acid has specific effects in the treatment of scurvy. Even small doses (*e.g.* 10 mg./day) will not only prevent scurvy but will cure the clinical features of ascorbic acid deficiency (Sheffield experiment). However, much larger doses are usually desirable in practice.

Ever since synthetic ascorbic acid first became available for clinical use in 1933 it has been recommended in an extraordinary number of conditions, including infective, allergic and toxic states of almost every kind. Yet apart from its action as a reducing agent in correcting the rare condition methæmoglobinæmia, its only proven use is in the treatment of ascorbic acid deficiency. This deficiency is due, in the great majority of cases, to dietary errors ; the first line of treatment is to supply the fresh fruits and vegetables that have been lacking, supplemented when necessary by concentrated natural sources of the vitamin (see Table 14, 1). If the patient is suffering from clinical scurvy, synthetic ascorbic acid in a dose of 250 mg. four times daily should be given during the first week of treatment. Synthetic ascorbic acid is also useful when, for one reason or another, the patient is unable to take a satisfactory diet or when an emergency suddenly occurs, such as a surgical operation which requires prompt correction of the deficiency. Synthetic ascorbic acid is cheap and harmless even in large doses, since any excess taken is very rapidly lost in the urine.

THIAMINE—VITAMIN B_1

History

The first important step towards the isolation and synthesis of this vitamin was the discovery that a disease resembling beriberi could be produced in animals under laboratory conditions. In 1890 the Dutch physician Eijkman (1897), working in a military hospital in Java, fed some domestic fowls on the food provided for his patients suffering from beriberi. He noticed that they developed weakness of the legs and head retraction. Their food consisted mainly of polished rice ; a new head cook at the hospital discontinued this supply of ‘ military ’ rice, so that thereafter the birds had to be fed on whole-grain ‘ civilian ’ rice, with the result that they recovered. Many great advances in science have started from such chance observations pursued by men of inspiration. Eijkman deservedly won the Nobel Prize many years later for showing that there was something existing in very small amounts in the germ and pericarp of rice that protected fowls from a disease resembling beriberi, and for recognising the fact that it was an unknown nutrient. He extracted it from rice polishings with water and alcohol.

Thirty years later Jansen and Donath (1926), working in the same laboratory, succeeded in isolating this factor (thiamine) in crystalline form. They used small rice birds (*Munia maja*) instead of fowls for testing the activity of the different fractions which they prepared in the course of isolating the vitamin. Thiamine deficiency, they found, could readily be produced in this bird ; it was also produced in pigeons, rats and mice by numerous other workers who were seeking in the 1920's to identify and isolate the vitamin.

The isolation of the crystalline vitamin left the chemists with the difficult task of identifying its structure. It was found to contain a sulphur atom united in a hitherto unknown (thiazole) ring. However, its structure was finally elucidated and its synthesis accomplished by Williams and Cline (1936). Williams began his search for the vitamin in 1913 in the Philippines, under the guidance of E. B. Vedder, a pioneer in the clinical study of beriberi.

Thiamine Deficiency in Birds

The condition produced in birds by acute thiamine deficiency is characterised by head-retraction and convulsions indicating a disorder of the nervous system. It is clear that these features are due to an acute biochemical lesion in the brain, which is not necessarily associated with any anatomical lesion of the brain or peripheral nerves. The giving of pure synthetic thiamine rapidly relieves this biochemical lesion as is shown in Plate V (Peters, 1953) ; but any coexisting anatomical lesions in the peripheral nerves are not necessarily relieved, and may have other causes (Chapter 33).

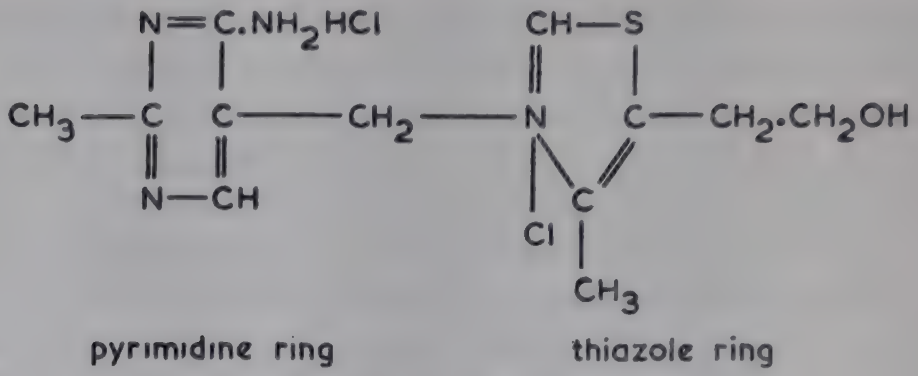
Nomenclature

When the vitamin that would prevent head-retraction in birds was finally isolated, Jansen named it ' aneurine,' implying its specific value to the nervous system. This name has now passed out of general use, since it was realised that the vitamin acts on all tissues and not only on those of the nervous system.

' Thiamine ' is the name originally given to the vitamin by Williams, following its synthesis. It obviates any suggestion of a specific biological property of the vitamin and is a reminder that it contains sulphur.

Chemistry

Thiamine chloride hydrochloride is a white crystalline substance with the formula shown at the top of next page.



thiamine chloride hydrochloride

It is readily soluble in water, but not in most fat solvents nor in fats. It is rapidly destroyed by heat in neutral or alkaline solutions ; in acid solution, however, it is resistant to heat up to 120° C. Thiamine can be converted by controlled oxidation into an inactive product, thiochrome, which is strongly fluorescent in ultraviolet light. This property is used for the chemical estimation of the vitamin in biological materials.

Physiological Activity

Thiamine was the first vitamin whose precise activity in the body was stated in biochemical terms. This was achieved by the work of Sir Rudolph Peters and his school at Oxford. In 1929 Peters and Kinnersley demonstrated an accumulation of lactic acid in the brains of thiamine-deficient pigeons. It was found that minced brain tissue from such birds took up less oxygen than brain tissue from normal birds in the presence of added glucose or lactic acid *in vitro* (Gavrilescu *et al.*, 1932). This failure of oxidation could be corrected by adding thiamine in catalytic amounts to the brain tissue. It was thus established for the first time that a vitamin could be an essential part of an enzyme system. At the start it seemed likely that thiamine was specifically concerned with lactic acid, but it was found that lactic acid was not the substance oxidised (Meiklejohn, 1933). Further research showed that pyruvic acid accumulated in the brain (Peters & Sinclair, 1933) and blood of such birds (Thompson & Johnson, 1935) and it was soon proved that thiamine is specifically concerned with its removal. The details of this research have been described by Peters (1953). It is now known that the pyrophosphate of thiamine is the coenzyme of carboxylase, the enzyme concerned with the decarboxylation and oxidation of pyruvic acid.

The fact that thiamine is concerned with a stage in the breakdown of carbohydrate explains how signs of deficiency of the vitamin develop most rapidly in animals fed diets rich in carbohydrates. The onset of deficiency is delayed by a diet rich in fat. There is evidence from dietary surveys that the same may also be true in man.

The brain and nerves have a constant respiratory quotient of unity, which shows that their energy is derived solely from the oxidation of carbohydrate. The role of thiamine in the breakdown of carbohydrate explains how deficiency in animals leads rapidly to a biochemical lesion in the brain.

The total amount of thiamine in the well-nourished human body is small, amounting in all to about 25 mg. The highest concentration is found in the heart, brain, liver, kidneys and skeletal muscles. The body has no means of storing any excess so that no benefit derives from taking large doses ; the excess is lost in the urine.

Experimental Deficiency in Man

Human volunteers have been fed on diets deficient in thiamine but adequate in other respects (Williams *et al.*, 1942 ; Keys *et al.*, 1945). The first reported symptoms have usually been loss of appetite (anorexia) and mental changes resembling anxiety states, with irritability and easy exhaustion. To what extent these are specific effects of the deficiency is open to question. They may be the non-specific result of an unaccustomed regime and a distasteful diet. Thus an experiment conducted in Great Britain during the second world war (Medical Research Council, 1947) differed from those in America in that the diet did not exclude foods containing thiamine and was therefore normal in composition and appetising. The thiamine content of the diet was reduced to 0·3 mg. daily by cooking with sodium bicarbonate those foodstuffs which were the principal sources of the vitamin. The twelve young men who volunteered for this experiment were seen at regular intervals during the three months that they continued on the diet. Not only did none of them develop anorexia, but they showed no definite symptoms or signs that could clearly distinguish them from twelve normal controls receiving the same diet supplemented with thiamine pills. It must be concluded that previously healthy people can subsist without trouble for several months on an intake of thiamine considerably below the usual recommended allowances.

Laboratory Diagnosis

In urine thiamine can be estimated by oxidising it to thiochrome and measuring the latter by means of the intensity of its fluorescence in ultraviolet light. But the amount of thiamine in the urine is no reliable test of deficiency, since it falls to low levels as soon as the dietary intake is reduced and before the tissues are depleted. To overcome this difficulty various ‘ saturation tests ’ have been proposed, based on giving one or more doses of the vitamin and measuring the dose or time needed to produce a large increase in urinary excretion. But such methods also have their drawbacks ; if a single large dose is given, much of it escapes in the urine before the tissues have time to take it up. The free vitamin is very soluble and freely diffusible ; the kidneys have no threshold for retaining it ; consequently much can be lost in the urine even in states of deficiency, particularly if given by intravenous injection.

A satisfactory laboratory test must show whether a patient's symptoms can reasonably be attributed to lack of thiamine. Tests that merely indicate the degree of tissue reserves of the vitamin, even if they are reliable, are inadequate for this purpose. The point at which a dietary deficiency of the vitamin becomes important is when it is sufficiently severe to cause a biochemical lesion interfering with the normal metabolism of carbohydrate. This lesion results in the accumulation of pyruvic acids in the tissues and also in the blood. The rise in the level of this acid in the blood of patients with Oriental beriberi was first shown by Platt and Lu (1936) in 1936. This useful test has since been made more sensitive by measuring the accumulation of pyruvic acid in the blood following exercise or an oral dose of glucose (Thompson, 1957). It should be realised, however, that thiamine deficiency is by no means the sole cause of an elevated blood pyruvic acid ; the test is not specific unless accompanied by a therapeutic trial, demonstrating improvement following the administration of thiamine.

DIETARY SOURCES

All animal and plant tissues contain thiamine and it is therefore present in all whole natural foods ; but the only important stores in the biological world are in the seeds of plants. The germ of cereals, nuts, peas, beans and other pulses and in addition yeast, are the only rich sources. All green vegetables, roots, fruits, flesh foods and dairy produce (except butter) contain significant amounts of the vitamin, but none are rich sources. As the vitamin is not soluble in fats, it is not found in butter or in any separated vegetable or animal oil. Pork resembles human flesh in having a higher content of thiamine than beef or mutton. In the refining of sugar and many cereal products all the naturally occurring vitamin may be removed : there is also none in distilled spirits. The distribution of the vitamin within cereal grains and the effect of milling and other food processing are discussed in Chapter 17. The thiamine content of some common foods is given in Table 14, 2.

As thiamine is readily soluble in water, considerable amounts may be lost when vegetables are cooked in an excess of water which is afterwards discarded. It is relatively stable to temperatures up to boiling point, provided that the medium is slightly acid, as in baking with yeast. But if baking powder is used, or if soda is added in the cooking of vegetables, almost all the vitamin may be destroyed. The loss of thiamine in the cooking of an ordinary mixed diet is usually about 25 per cent. Modern processes for freezing, canning and dehydrating food result in only small losses.

RECOMMENDED ALLOWANCES

While there is a clearly demonstrated relationship between the utilisation of thiamine and the amount of carbohydrate in the diet of animals, efforts to prove that the thiamine requirements of man depend

TABLE 14, 2. *Sources of thiamine*

Source	Description	Thiamine	
		mg./1000 Cal.	mg./100 g.
Satisfactory or rich sources not usually associated with beriberi—			
Whole wheat	...	1·2	0·4
Pulses	Various	1·2	0·4
Millets	Sorghum	1·2	0·4
Rice	Home pounded	0·35*	0·08–0·14*
Rice	Parboiled and milled	0·32*	0·11*
Poor sources associated with beriberi—			
White bread	70 per cent. extraction flour	0·20	0·05–0·07
Rice	Raw, milled	0·15*	0·02–0·04*
Sugars and jams	...	0	...
Corned beef	...	0	...
Moderate sources protective against beriberi if consumed in large amounts—			
Fruits and vegetables	Fresh	0·5–1·2	0·02–0·20
Pork	Fresh	1·0–1·5	0·72–1·04
Beef	Fresh	0·3–0·5	0·07–0·30
Mutton	Fresh	0·5	0·16–0·20
Fish	Fresh	0·3–1·0	0·01–0·10
Milk	Cow's	0·7	0·04
Eggs	...	1·0	0·10–0·15
Rich sources used in the treatment of beriberi—			
Yeast †	Brewers', dried	...	6–24
Bran	Rice or wheat	...	2–4
Marmite	Yeast extract	...	2·4–3·0

Note.—Butter, vegetable oils and other fats contain no thiamine, but as the vitamin is not needed for their metabolism they are not beriberi-producing.

* Assuming losses of 50 per cent. in washing and cooking.

† Bakers' yeasts have much less thiamine than brewers' yeast and are unreliable for therapeutic purposes.

on the relative proportion of carbohydrate to fat in the diet have not met with entirely convincing results. Nevertheless, in calculating recommended allowances of the vitamin for human subjects, it has become usual to relate the thiamine intake to the 'non-fat' (carbohydrate and protein) calories consumed. The Committee on Nutrition of the British Medical Association (p. 254) recommended a daily allowance of 0·6 mg./1000 non-fat Cal. (or 0·4 mg./1000 total Cal.) for every kind of consumer except nursing mothers. For nursing mothers taking 3000 Cal./day this Committee recommended sufficient supplements to bring the thiamine intake to a total of 1·4 mg./day. These amounts are certainly sufficient for healthy people living on the varied type of diet that is now usual in Great Britain.

THIAMINE-CALORIE RELATIONSHIPS

It should be emphasised that Oriental beriberi is not a disease of famines. Indeed cardiovascular beriberi may occur among people with good supplies of polished rice and good appetites to eat it. It results from a poorly balanced diet. The concept of a desirable thiamine-calorie ratio for a diet is perhaps more useful than attempts to relate thiamine needs directly to carbohydrate intake. Whole wheat, for instance, has a ratio of about 1·2 mg./1000 Cal. and is actively protective against beriberi. Raw polished rice has a value of about 0·15 mg./1000 Cal. and so is beriberi-producing. Most fruits, vegetables and flesh foods have a ratio just above a critical level of about 0·25 and so are weakly effective in preventing beriberi.

Therapeutic Uses

Thiamine is life-saving in the treatment of cardiovascular and infantile beriberi and Wernicke's encephalopathy as discussed in Chapters 32 and 33. It may be given, though without expectation of dramatic results, in cases of nutritional neuropathy. There is no reliable evidence that it is useful in any other disorder of the nervous system. The prescription of synthetic thiamine, either alone or in combination with other vitamins, as a general tonic or appetiser, is supported by no good scientific evidence.

In prescribing thiamine it should be remembered that the healthy human body has only about 25 mg. of the vitamin in its entire structure. Furthermore, it has no means of storing any excess taken in the diet; the excess is lost in the urine with great speed. The human body is certainly a most effective machine for dissolving thiamine pills and transferring the solution rapidly to the urinal, but this is a costly procedure for whoever has to pay for it.

NICOTINIC ACID (NIACIN) AND NICOTINAMIDE

History

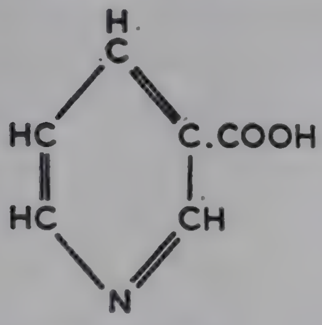
Nicotinic acid has been known to the organic chemists since 1867. As early as 1913 Funk (1913) isolated it from yeast and rice polishings in the course of an attempt to identify the water-soluble anti-beriberi vitamin. But interest in the acid was lost when it was found ineffective in curing pigeons of beriberi. Not till more than twenty years later did the acid again attract the interest of biochemists, though not initially because of its properties as a vitamin. In 1935 three independent groups of European biochemists demonstrated that the amide of nicotinic acid was a component part of the hydrogen acceptor, nicotinamide—adenine dinucleotide (NAD) concerned with tissue oxidation.

The recognition later that nicotinic acid is the ' pellagra-preventing ' (P-P) vitamin was achieved in the following manner. In the 1920's Goldberger and his colleagues in the United States Public Health Service recognised that human pellagra responded not only to treatment with animal protein but also to boiled extracts of yeast almost devoid of protein

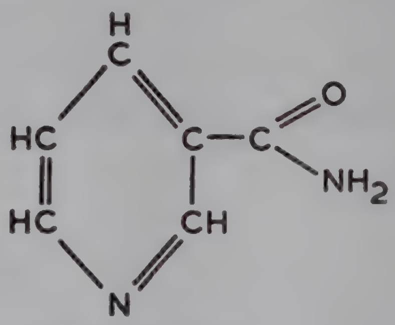
(Goldberger *et al.*, 1928). This naturally led to the supposition that the P-P factor was identical with 'heat-stable vitamin B_2' present in yeast. An important step towards the isolation of this factor was the discovery of a suitable laboratory animal for testing its potency in various concentrated preparations derived from natural sources ; it was found that a pellagra-like disease could be produced in dogs and pigs (Plate VI, Chick *et al.*, 1938). Following the discovery by Ruffin and Smith (1934) that a crude extract of liver was effective in human pellagra, and therefore a source of the P-P factor, Elvehjem and his colleagues (1937) finally isolated nicotinamide from liver as the factor that would cure black-tongue in dogs. Reports of the dramatic therapeutic effects of nicotinic acid in human pellagra quickly followed from several clinics.

CHEMISTRY

Nicotinic acid is a simple derivative of pyridine. Although related chemically to nicotine, it possesses very different physiological properties and is non-toxic, even in large doses. It is a white crystalline substance readily soluble in water and resistant to heat, oxidation and alkalis : it is in fact one of the most stable of the vitamins. Nicotinic acid is synthesised on a large scale commercially ; its chemical formula and that of its amide—in which form it occurs naturally in the body—are as follows :



nicotinic acid



nicotinamide

PHYSIOLOGICAL ACTIVITY

The essential activity of nicotinamide as a component of the NAD molecule, concerned with tissue oxidation, is described in Chapter 9. The lack of NAD in pellagra may account for the inflammatory changes that occur in the skin and gastrointestinal tract, though the precise mechanism involved is still obscure.

It has recently become evident that the human body is only partly dependent on dietary sources of nicotinic acid to maintain its content of NAD. There is much circumstantial evidence that nicotinamide can be synthesised in the human body from the amino acid, tryptophan. Part of this synthesis is probably accomplished through biosynthesis by micro-organisms in the intestines, but there may also be some direct synthesis in the tissues (Chick, 1951). This has important implications in deciding 'requirements' for nicotinic acid in the diet.

Horwitt and his colleagues (1956) have reported a useful study on the extent to which tryptophan can replace nicotinic acid in the diet. From their observations on a large group of patients they conclude that on average about 60 mg. of tryptophan are needed to replace 1 mg. of dietary nicotinic acid. It has been suggested that the nicotinic acid equivalent (the nicotinic acid content + tryptophan content) of a food or diet is a better measure than the nicotinic acid content alone. Figures for nicotinic acid equivalent are usually expressed in mg./1000 Cal. This appears sensible and removes one anomaly : milk and eggs are poor sources of nicotinic acid, although they have long been recognised as beneficial to patients with pellagra ; each of these foods has a high nicotinic acid equivalent.

Laboratory Diagnosis of Nicotinic Acid Deficiency

Attempts to diagnose this deficiency by laboratory methods have proved disappointing. Blood normally contains about 0·5 mg./100 ml. mainly as NAD, but in states of manifest deficiency the amount is not greatly reduced and nicotinic acid and its metabolic derivatives continue to be excreted in the urine.

Nicotinic acid can be estimated in blood and other biological material by a chemical technique (Swaminathan, 1938), based on a reaction with cyanogen bromide and aniline leading to the formation of a yellow colour. A microbiological method (Snell & Wright, 1941), in which the amount of lactic acid produced by *L. arabinosis* grown on synthetic medium is also reliable.

Dietary Sources

Nicotinic acid is widely distributed in plant and animal foods, but only in relatively small amounts, except in meat (especially the organs), fish, wholemeal cereals and pulses. In some cereals, such as maize, the greater part may be in a bound unabsorbable form, as demonstrated by Kodicek and his colleagues (1956) in feeding experiments on pigs. In a normal Western European diet about half the nicotinic acid content is provided by meat and fish.

Cooking causes little actual destruction of nicotinic acid but considerable amounts may be lost in the cooking water and ' drippings ' from cooked meat if these are discarded. In a mixed diet, from 15 to 25 per cent. of the nicotinic acid of the cooked foodstuffs may be lost in this way. Commercial processing and storage of foodstuffs cause little loss.

As a result of the wide distribution of nicotinic acid among foodstuffs and its stability to heat and storage, even a moderately good diet normally contains satisfactory amounts. Yeast and bran are good natural sources of the vitamin, but the removal of the bran in the milling of wheat reduces the nicotinic acid content of white wheaten flour to a low level.

RECOMMENDED ALLOWANCES

It is impossible to establish any precise figure for the amount of nicotinic acid (as determined by biochemical analysis) that a diet should provide. The amount needed in the diet must depend in part on the amount of good quality protein supplying tryptophan, from which the body can synthesise the vitamin. In the opposite way some foods--notably maize—contain nicotinic acid in a form that cannot be absorbed.

TABLE 14, 3. *Natural sources of nicotinic acid*

Food	Description	Range (mg./100 g. edible portion)
Good sources—		
Wheat bran	Outer bran only	25·0–46
Wheat-germ meal	Germ fraction finely ground	3·0–7·0
Millets	Various	1·3–3·2
Rice	Lightly milled	4·0–4·5
Sorghum	...	2·5–3·5
Wheat flour	Wholemeal	4·0–5·5
Fish	Fresh and cured	2·0–6·0
Beef, mutton, pork	...	3·0–6·0
Liver and kidney	...	7·0–17·0
Brewers' yeast	...	30·0–100·0
Meat extract	...	38·0–103·0
Bemax	...	5·7
Marmite	...	60·0
Moderate sources—		
Maize	Whole	1·5–2·0
Oatmeal	...	0·9–1·3
Rice	Highly milled	1·0–1·6
Wheat flour	70 per cent. extraction	1·0
Wheat flour	British (1956) regulation	1·5
Pulses	...	1·5–3·0
Cashew nuts	...	2·0
Fruit	Dried	1·0
Cocoa powder	...	1·0–1·5
Chocolate	Plain	1·0
Poor sources—		
Maize	Meal	0·2–1·5
Potato	...	1·0
Green leafy vegetables	...	0·2–1·5
Vegetables	Assorted—30 per cent. green	0·5
Fruits	Fresh tropical and temperate	0·2–1·5
Eggs	Fresh	0·1
Milk	Fresh, cow's	0·1
Cheese	...	0·03

The Committee on Nutrition of the British Medical Association (1950) recommended an allowance of from 4 to 20 mg./day, depending on the caloric intake, although admitting that the relationship thereto is 'hardly more than suggestive.' These allowances (given in Table 15, 1) are certainly generous ; it seems likely that the essential needs of an adult on a good mixed diet are not more than 10 mg. of nicotinic acid daily.

THERAPEUTIC USES

Nicotinic acid and nicotinamide have specific and dramatic effects in pellagra. The acid, though not the amide, causes transient vasodilatation when taken by mouth, resulting in flushing, burning and tingling, especially round the neck, face and hands. This reaction lasts, at most, only a few minutes. Nevertheless nicotinic acid has been widely used as a vasodilator drug in chilblains and other vascular disorders. It has also been tried as a drug in a wide variety of other diseases, mostly quite unconnected with nutritional failure. However, after over 20 years of trial the only proven therapeutic usefulness of nicotinic acid is in the treatment of primary deficiency, as occurs in pellagra, or in the conditioned deficiency as occurs in malabsorption syndromes.

RIBOFLAVIN

HISTORY

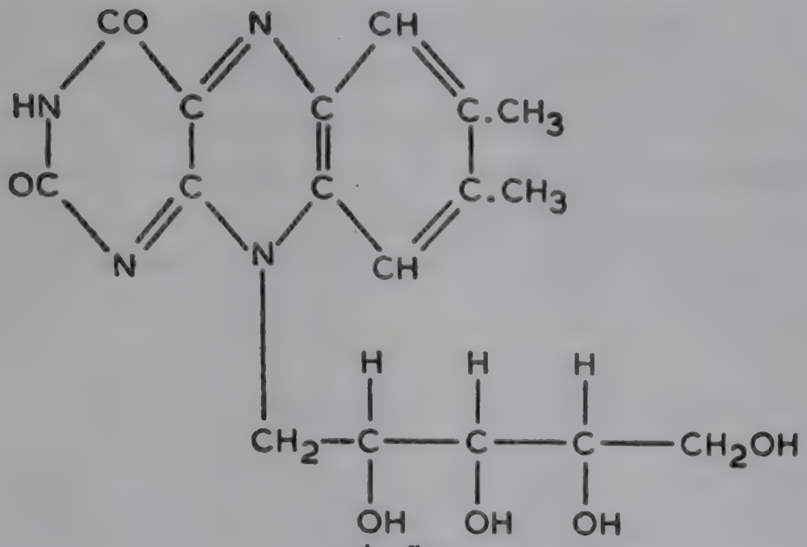
Riboflavin was discovered in the course of the search for the hypothetical 'heat-stable vitamin B_2.' Identifying this vitamin by means of its growth-promoting properties in rats, Kuhn and his colleagues (1933) finally isolated the factor from milk ; from 5400 *l.* of whey they extracted 1 g. of crystalline riboflavin. It was soon found, however, that riboflavin did not have all the properties previously ascribed to vitamin B_2, *e.g.* it did not cure black-tongue in dogs. Evidently, therefore, riboflavin was only one of several factors present in the heat-stable fraction of the vitamin B complex.

An important clue to the nature of Kuhn's crystals was that they were yellow in colour. One year previously Warburg and Christian (1932) had described their 'yellow enzyme' a respiratory catalyst capable of acting as a carrier for molecular hydrogen. They obtained it from extracts of yeast and went on to show that it consisted of a protein component combined with a yellow pigment, neither of which alone was enzymically active, though effective in combination. It was an inspired guess that the yellow pigment of Warburg's enzyme was identical with the new vitamin, for so it proved to be.

Only two further years elapsed before riboflavin was synthesised in 1935 by two independent groups of workers under Kuhn in Heidelberg and Karrer in Basle.

CHEMISTRY

Riboflavin is a yellow crystalline substance slightly soluble in water but not in fats, composed of an alloxazine ring structure linked to an alcohol derived from the pentose sugar ribose, as shown at the top of the opposite page.



riboflavin

Though stable to boiling in acid solution, in alkaline solution it is readily decomposed by heat. It is also destroyed by exposure to light. In plant and animal tissues riboflavin is linked with phosphoric acid to form a mononucleotide. This in turn is combined with certain proteins to form the catalytically active flavoproteins or 'yellow enzymes,' which are capable of reversible oxidation and reduction. In some of the flavoproteins the flavin nucleotide is linked with an adenine nucleotide to form a flavin adenine dinucleotide (FAD). The structure of the flavoproteins also varies with the nature of the specific protein to which the mononucleotide or dinucleotide is attached. Some nine different flavoproteins have been identified by their individual and distinctive catalytic behaviour.

PHYSIOLOGICAL ACTIVITY

Riboflavin acts in the body as the coenzyme or active prosthetic group of the flavoproteins which are concerned with tissue oxidation as described in Chapter 9.

Riboflavin deficiency in animals results in a failure to grow ; it was this effect that led to the first isolation of the vitamin. In rats the skin, and particularly the eyes, are affected.

Riboflavin and the eye.—The normal cornea has no blood supply. The scattered cells that maintain the integrity of its transparent collagenous structure are remarkable in their ability to survive without the aid of circulating hæmoglobin in their immediate vicinity. This suggests that these cells may be especially dependent on the maintenance of efficient intracellular oxidation involving the flavoproteins and requiring an ample supply of riboflavin. It is certainly a matter of no surprise that the tears that bathe the surface of the cornea contain considerable amounts of riboflavin (Philpot & Pirie, 1943), nor that riboflavin deficiency in rats results in the invasion of the cornea by capillary blood vessels (Bessey & Wolbach, 1938). In vitamin A deficiency the ducts of the tear glands become blocked with plugs of keratin and—in rats at least—this is accompanied by a vascularisation of cornea that is indistinguishable from that produced by riboflavin deficiency. It seems possible that lack of vitamin A may produce in this way a secondary or conditioned deficiency of riboflavin in the cornea. Whether this is ever a factor in the production of human keratomalacia (Chapter 35) is a question that must await more clinical study and research, but in the meantime it is certainly wise that sufferers from this grave disease should be treated not only with vitamin A but also with riboflavin.

DEFICIENCY OF RIBOFLAVIN IN MAN

Sebrell and Butler (1938) described the clinical effects of feeding human subjects for four months on a diet providing about 0·5 mg./day of riboflavin. Their subjects developed angular stomatitis, cheilosis and nasolabial seborrhœa which responded to the administration of riboflavin. Two years later Sydenstricker and his colleagues (1940) first described among pellagrous patients in the Southern U.S.A. an invasion of the cornea by capillary blood vessels similar to that seen in rats suffering from riboflavin deficiency. This ocular lesion, accompanied by lachrymation and photophobia, was often associated with angular stomatitis and other features of the orogenital syndrome (Chapter 37). These lesions responded to the administration of riboflavin. However, it should be realised that other factors besides riboflavin deficiency can cause corneal vascularisation and angular stomatitis.

In view of the importance of riboflavin in cellular respiration it seems surprising that the clinical changes attributed to its deficiency are minor and do not by themselves threaten life. The ability of the human species to survive and multiply has depended on a variety of biological adaptations, one of which, perhaps, has been the ability to dispense with a regular dietary supply of the vitamin. Even though riboflavin has a wide distribution in the foodstuffs used by man there are still many people who live for long periods on a very low intake.

LABORATORY DIAGNOSIS

In the presence of ultraviolet light riboflavin has a brilliant greenish-yellow fluorescence which provides a means of detecting and estimating small quantities in extracts of biological materials. It is more easily estimated by bio-assay, using its growth-promoting properties for certain micro-organisms. These methods have been of value in measuring the riboflavin in foodstuffs, in human urine and fæces, and in the tissues of animals. As yet, however, they have found no practical application in clinical diagnosis.

DIETARY SOURCES

The best sources of riboflavin are liver, milk, eggs and green vegetables. It differs from other components of the vitamin B complex in that it occurs in good amounts in dairy produce, but is relatively lacking in cereal grains. It is also present in beer. Ordinary methods of cooking do not destroy the vitamin apart from losses that occur when the water in which green vegetables have been boiled is discarded. If foods, especially milk, are left exposed to sunshine, large losses may occur. Especially good sources of the natural vitamin are yeast extract (*e.g.* Marmite) and meat extract (*e.g.* Bovril). Table 14, 4 gives the riboflavin content of some common foods.

TABLE 14, 4. *Natural sources of riboflavin*

Food	Description	Range (mg./100 g. edible portion)
Good sources—		
Wheat bran	Bran layer only	0·5
Wheat and barley	Whole grain	0·12–0·25
Wheat germ	Germ fraction, steam-heated and finely ground	0·25
Pulses	Various, fresh	0·1–0·3
Fish	Various, fresh and cured	0·2–0·4
Beef, mutton and pork	Raw	0·10–0·3
Liver and kidney	...	0·7–3·3
Eggs	Fresh	0·3–0·5
Cheese	...	0·5
Cocoa	Powder	0·3–0·4
Chocolate	Plain	0·2
Brewers' yeast	...	1·3–4·0
Yeast extract, *e.g.* Marmite	...	5·0–6·0
Wheat germ, *e.g.* Bemax	...	0·67
Meat extract, *e.g.* Bovril, Oxo	...	1·8–2·6
Moderate sources—		
Maize	Whole	0·1
Oatmeal	...	0·15
Sorghum	...	0·10–0·15
Wheat flour	Wholemeal (*i.e.* containing germ and fine bran)	0·10–0·15
Cashew nuts	...	0·2
Green leafy vegetables *	...	0·05–0·50
Fruit	Dried	0·1
Milk	Fresh cows'	0·15
Beers	...	0·05–0·10
Poor sources—		
Maize	Meal	0·02–0·1
Rice	Lightly milled	0·05–0·1
Rice	Highly milled	0·03–0·05
Wheat flour	70 per cent. extraction	0·03–0·05
Fruits	Fresh, tropical and temperate	0·01–0·1
Potato	All seasons	0·05
Vegetables	Various—30 per cent. green	0·09

* Green vegetables and fruits in tropical countries are, in general, richer in riboflavin than those common in temperate regions.

RECOMMENDED ALLOWANCES

The amount of the vitamin that the body needs in the diet to replace daily losses has not been accurately determined for any class of individual.

If bacterial biosynthesis in the intestines is an additional source, the nature of the diet in other respects may determine the growth and types of micro-organisms and the amount of surplus riboflavin they produce. A well-balanced diet containing a satisfactory supply of other necessary nutrients usually provides from 1 to 2 mg./day of riboflavin. Most authorities recommend a daily allowance of about this order. There have been attempts to state ' requirements ' with more precision, distinguishing between the needs of different categories of people on the basis of age, sex, caloric and even thiamine intake, assigning to each a ' requirement ' stated to within a tenth or even a hundredth of a milligram. Such attempts lend an appearance of accuracy to essentially inaccurate information. The true requirements for riboflavin are best satisfied by the provision of a good mixed diet.

Therapeutic Uses

Synthetic riboflavin, both for oral and parenteral administration, is readily available, but its therapeutic uses are not well supported by objective clinical evidence, despite a vast amount of honest propaganda in its favour. It may be tried empirically in cases of angular stomatitis and the other lesions that sometimes coexist, especially if they occur in cases of the malabsorption syndrome, in which there are reasons for thinking that the absorption of riboflavin may be impaired. Those who wish to prescribe this vitamin may give it by mouth in doses of 5 mg. three times daily. There is no evidence that larger doses will produce any further benefit or that parenteral administration is ordinarily to be preferred.

When the full history of the vitamin comes to be written it may well be shown that the identification and synthesis of riboflavin was of more ultimate interest to biochemists than to physicians.

Toxic Effects

Thus far, no one seems to have been adversely affected by treatment with synthetic riboflavin.

THE ANÆMIA-PREVENTING VITAMINS

Historical Introduction

Scarth Combe (1824) of Edinburgh was probably the first to suggest that ' pernicious ' anæmia might be a conditioned nutritional disorder. He thought that " idiopathic anæmia might be a circumstance denoting imperfect assimilation of nourishment." Pernicious anæmia, as first fully described by Addison in 1849, is a disease that occurs rarely and sporadically in most human races, apparently without relation to dietary habits. A constitutional or genetic predisposition to the disease was early recognised. As its name implies, the disease was uniformly fatal and as much to be feared as any cancer until Minot and Murphy (1926) demonstrated the value of whole liver by mouth in its treatment. This was soon followed by the classic experiments of Castle (1929) who showed that beef muscle mixed with normal gastric juice caused new blood formation in patients with pernicious anæmia, though neither was effective alone. He called the unknown factor in gastric juice ' intrinsic factor ' and that in beef muscle ' extrinsic factor,' suggesting at the same time that the two interact to produce the remedial substance present in liver. These experiments were the forerunners of all subsequent work on the disease. Later it was found that the need for intrinsic factor could be circumvented, not only by giving large amounts of liver by mouth but also by injecting extracts of liver intramuscularly. Thereafter the search for the hypothetical ' anti-PA ' vitamin was directed towards its isolation from extracts of liver. The search was hampered by the fact that the potency of each new concentrate of liver could only be gauged by direct therapeutic trials on human patients with Addisonian anæmia. Unlike some other vitamins, no animal was found in which deficiency of the anti-PA vitamin could be induced and studied in the laboratory. The lack of a suitable animal to assist in laboratory trials undoubtedly delayed the discovery of cyanocobalamin. The history of the early work on Addisonian anæmia has been reviewed by Davidson and Gulland (1930).

Then, as has happened repeatedly in the history of the vitamins, a new and unexpected development came from a totally unrelated field of biochemistry. Folic acid had been isolated as a factor necessary for the growth of certain micro-organisms (p. 243.) In Addisonian anæmia folic acid resulted in dramatic therapeutic responses. It soon became apparent, however, that although synthetic folic acid (pteroylglutamic acid, PGA) corrects (at least temporarily) the defect in the formation of red blood corpuscles in Addisonian anæmia, it had no influence in preventing or curing the degenerative changes in the nervous system which are often a serious feature of the disease. The ' anti-PA ' vitamin of liver extract, cyanocobalamin, was finally isolated in 1948.

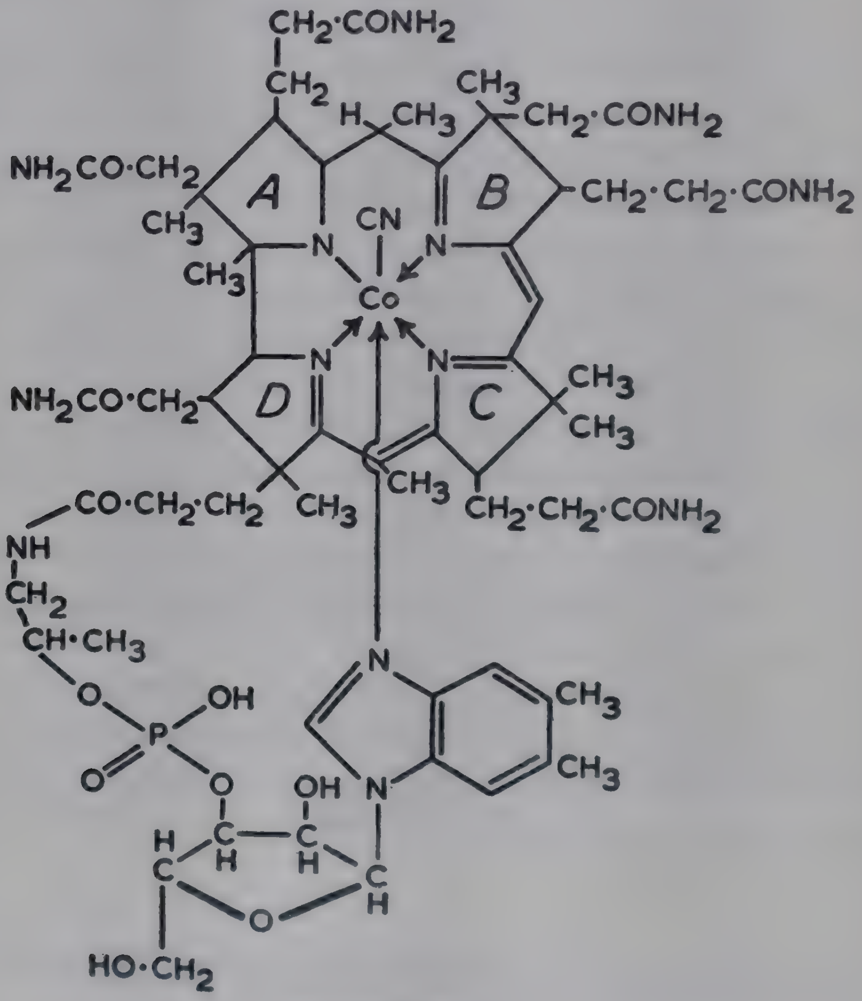
VITAMIN B_{12}—CYANOCOBALAMIN AND RELATED SUBSTANCES

History

The discovery that protein-free extracts of liver, given by injection, were effective in Addisonian anæmia, led to many attempts over a period of twenty years to isolate from liver the active principle concerned. Progress was necessarily slow through lack of any easy means of detecting the vitamin until Mary Shorb made the useful discovery that liver extracts effective in Addisonian anæmia had growth-promoting properties for the micro-organism *Lactobacillus lactis dorner*. The search for the growth factor for this organism thereafter proceeded rapidly and, aided by the fact that it was found to have a red colour, the isolation of crystalline vitamin B_{12} was achieved almost simultaneously in Great Britain (Smith & Parker, 1948) and the U.S.A. (Rickes *et al.*, 1948). Proof soon followed of the effectiveness of this crystalline factor in the treatment of both the hæmatological and neurological manifestations of Addisonian anæmia. For a review article with many references the reader is referred to Gräsbeck (1960).

CHEMISTRY

About 1 ton of fresh liver was needed for the isolation of 20 mg. of the red crystals. These were found to have a molecular weight of about 1350 and to contain, surprisingly, 4 per cent. of the mineral element cobalt, which previously was known to be an essential nutrient for sheep and cattle. The crystalline material was given the specific name—cyanocobalamin. It is freely soluble in water and resistant to boiling in neutral solution though unstable in the presence of alkalis. It may decompose on storage, especially in the presence of other organic materials as in crude liver extract.



cyanocobalamin

The chemical nature of the vitamin was elucidated by two teams working in co-operation under Dorothy Hodgkin at Oxford (Hodgkin *et al.*, 1955) and under Sir Alexander Todd at Cambridge (Bonnet *et al.*, 1955). The cobalt is contained in a porphyrin-like ring which is linked to a nucleotide containing a base, ribose and phosphoric acid. In nature, B_{12} usually occurs in combination with protein, to which it is linked in several places.

Vitamin B_{12} is present in the body in several forms, including hydroxocobalamin. This is available commercially and is stated to be as effective as cyanocobalamin in the same dosage. It is claimed to have the advantage of being retained in the body much longer than cyanocobalamin and hence may become the preparation of choice. The vitamin is produced commercially as a cheap by-product of the cultivation of *Streptomyces griseus* used in the preparation of the antibiotic streptomycin.

Physiological Action

A useful review of this subject has been provided by Girdwood (1957). The essential biochemical lesion in Addisonian anæmia is not as yet fully understood. It probably affects every cell in the body but its deficiency is most severely felt in tissues where the cells are normally dividing rapidly, *e.g.* in the blood-forming tissues of the bone marrow and in the gastrointestinal tract. The nervous system is also affected, perhaps because of its limited range of metabolic pathways and essential dependence on carbohydrate catabolism. The biochemical lesion results in an arrest in the development of new red blood corpuscles and sometimes causes degeneration of nerve fibres in the spinal cord and peripheral nerves. The effect of the deficiency can be detected by microscopic examination of samples of bone marrow. Abnormal cells—megaloblasts—are seen. These are larger than the nucleated cells that give rise to normal red blood corpuscles. Their large reticulated nuclei may well be the result of an abnormality in nucleic acid metabolism. When megaloblasts are present in the bone marrow the circulating red cells derived from them are bigger than normal (macrocytic) though usually carrying a normal concentration of hæmoglobin (normochromic).

Quite clearly, vitamin B_{12} participates in some essential enzyme system or systems since the amount needed to transform a patient dying of Addisonian anæmia into a healthy person is amazingly small. From the nucleotide structure of the vitamin it is a reasonable guess that it is concerned with nucleic acid metabolism whilst its porphyrin-like ring suggests an association with the intracellular porphyrin-containing respiratory enzymes.

Assimilation of vitamin B_{12}

There is no doubt now that vitamin B_{12} is the 'extrinsic factor' originally postulated by Castle, but it still remains to be explained exactly why a normal gastric secretion is needed for its proper utilisation. As Castle himself (1955) has said: " . . . It can be stated with assurance that pernicious anæmia is usually an example of a highly specific isolation of the affected person from his alimentary environment. Thus his disease would not develop if the patient could effect daily the transfer of a millionth of a gram of vitamin B_{12} the distance of a small fraction of a millimetre across the intestinal mucosa and into the blood stream. This he cannot do, principally as a result of failure of his stomach to secrete into its lumen some essential but still unknown substance." The normal requirements of an adult to prevent signs of deficiency are probably less than 1 μg./day (Gräsbeck, 1960). When micrograms of radiocyanocobalamin are given to patients with pernicious anæmia by mouth, little absorption, if any, occurs. When milligrams are given, a very small percentage of the dose is absorbed but probably a sufficient quantity to prevent deficiency. This may be due to simple diffusion. For the absorption of physiological doses and also of the vitamin present in foods, intrinsic factor is essential. It is perhaps a mucoprotein which may bind the vitamin and so allow absorption. However, neither the nature nor the mode of action of intrinsic factor is as yet established. Only very small amounts are needed.

The tapeworm, *Diphyllobothrium latum*, whose alternative hosts are the edible fish of the sea, infests particularly people in Finland and Iceland. The worms take the vitamin from the food into their own bodies. Thus infestation makes the vitamin unavailable and many of those infested have a conditioned megaloblastic anæmia. The small intestine in a healthy individual is either sterile or contains only a very small bacterial flora. In a variety of intestinal diseases (*e.g.* the malabsorption syndrome) there may be a large bacterial content. This may affect absorption of vitamin B_{12}, probably because the bacteria assimilate it from the food. The bacteria in the colon can assimilate the vitamin and may perhaps be able to synthesise it. Even in Addisonian anæmia enough vitamin B_{12} may be isolated from the patient's fæces to provide a curative dose, if given by injection. It therefore seems improbable that the bacterial inhabitants of the intestines contribute to the nutrition of their host by the biosynthesis of absorbable vitamin B_{12}.

The 'animal protein factor'

It has been known for a long time that certain animals grow faster if their diet contains small amounts of foodstuffs derived from animal sources; this is true even of essential vegetarians like the guinea-pig. This phenomenon cannot be explained solely as due to the lack of some specific amino acid. The very small amounts of animal foodstuffs required suggests the presence in them of some unidentified vitamin. It now seems clear that at least a part of the beneficial effects attributed to this factor is due to vitamin B_{12} in foods of animal origin.

EXPERIMENTAL DEFICIENCY IN MAN

A completely vegetarian diet, containing no milk, eggs or other foods of animal origin, is practically devoid of cobalamins provided that all its components are fresh and free from fermentation by micro-organisms. People who voluntarily follow such a diet have occasionally developed megaloblastic anæmia or more commonly developed neurological manifestations of vitamin B_{12} deficiency.

LABORATORY DIAGNOSIS

The total amount of vitamin B_{12} (in terms of cyanocobalamin) in the healthy human body is probably of the order of 5 mg. No chemical method could possibly estimate the very small amounts that occur in the blood and urine, but its remarkable growth-promoting properties for certain micro-organisms provide a means of estimation by biological methods. By this means the level of vitamin B_{12} in the blood, urine and tissues can be estimated. The serum of patients with pernicious anæmia during a relapse usually contains less than 100 $\mu\mu$g./ml., whereas in normal persons the level varies from 100 to 1000. The capacity of the bowel to absorb cyanocobalamin is a valuable test used in the investigation of complex cases of megaloblastic anæmia. If a 1 μg. dose of radioactive B_{12} is given to healthy persons, only about 30 per cent. is recovered in the fæces, whereas over 70 per cent. is recovered in patients with pernicious anæmia. The measurement of the urinary excretion of the isotope is another valuable test. The diagnosis of vitamin B_{12} deficiency by such methods is now a standard research procedure (Girdwood, 1956).

DIETARY SOURCES

The cobalamins are present only in foodstuffs of animal origin and in micro-organisms—bacteria and moulds—which alone seem capable of synthesising them and are probably the sole original source. Foods that are treated by prior bacterial fermentation or ' ripening ' may perhaps acquire vitamin B_{12} activity thereby. The plant kingdom generally seems to have no need for the cobalamins with the exception of seaweeds and algæ which presumably acquire them from bacteria. The common vegetables in human diets contain insignificant traces of vitamin B_{12}. However, when plant tissues undergo fermentation in the rumen of an herbivorous animal, the bacteria responsible for the fermentation produce considerable amounts of vitamin B_{12} which afterwards becomes available to the animal. Unfortunately man has no rumen, and as pointed out above, the bacteria that inhabit the colon do not subserve the same useful function.

Recommended Allowances

It is impossible as yet to state any figure for a desirable daily intake of vitamin B_{12}, especially in view of the uncertainty that exists about the possible influence of the intestinal flora on its biosynthesis and absorption. One thing, however, is certain, namely, that since a remission can be brought about in pernicious anæmia by the injection of 1 μg. of vitamin B_{12} daily, the human body requires only minute amounts to maintain its health, provided that there is a normal secretion of intrinsic factor by the stomach.

Therapeutic Uses

Cyanocobalamin, given by injection, provides complete and satisfactory treatment in cases of Addisonian anæmia. The general practice is to give 1000 μg. by injection twice in the first week of treatment and thereafter 250 μg. at weekly intervals until a normal blood level is attained. Subsequently an injection of 250 μg. every 3 weeks is all that is needed to keep the patient in health. These doses may appear excessive as much of the vitamin is excreted in the urine. Nevertheless they are justified because of the need to build up the body's depleted stores to normal as quickly as possible, and because vitamin B_{12} is now very cheap.

Uses as a growth factor

Cyanocobalamin has been used as the ' animal protein factor ' in farm husbandry. More frequently antibiotics such as aureomycin and penicillin are used. Apparently they act by inhibiting the growth of intestinal organisms which destroy the vitamin. So effective is the action of these substances that their use for accelerating the growth of pigs and fowls is now a commercial proposition in some circumstances. Apparently they promote the retention of nitrogen and so raise the biological value of vegetable proteins.

Naturally a similar action in malnourished children living on diets containing little or no animal proteins might be expected. However, three trials have now been carried out with scrupulous attention to technique, and with adequate controls, on children in Jamaica (Mackay *et al.*, 1956), South India (Someswara *et al.*, 1955) and Central America (Scrimshaw & Guzman, 1953). In each trial the children were living on poor vegetarian diets associated with impaired growth rates. In Jamaica and South India the vitamin and antibiotics had absolutely no effect. In some groups in Central America some slight acceleration of growth apparently occurred, but at a low statistical level of significance. The use of these substances is not likely to make an important contribution to child health in the tropics.

FOLIC ACID—PTEROYLGLUTAMIC ACID (PGA) AND RELATED SUBSTANCES

History

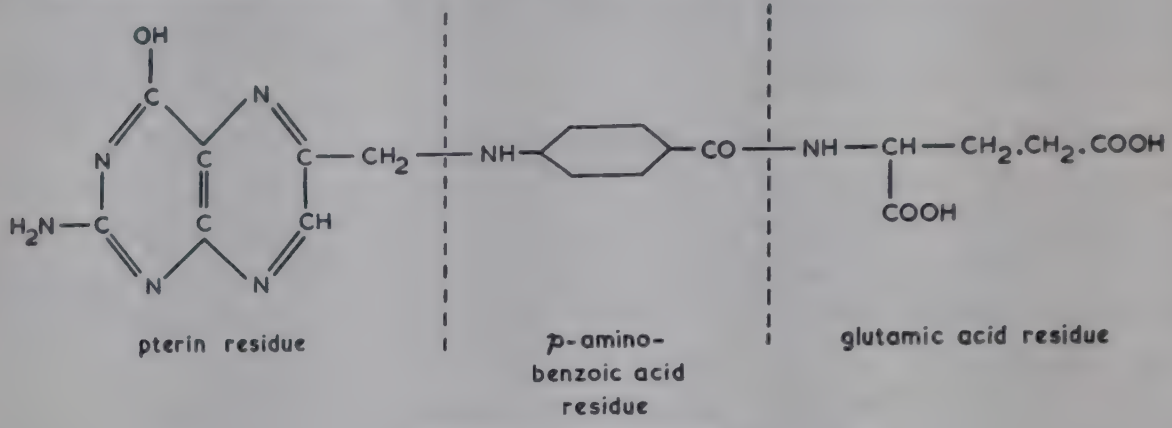
The classical studies of Dr Lucy Wills (1931) in Bombay drew attention to the importance of nutritional megaloblastic anæmia in pregnant women (Chapter 36). She also reproduced this anæmia in monkeys by means of a diet composed chiefly of polished rice and white bread, similar to that eaten by her patients. This anæmia did not respond to any vitamin known at that time, nor to purified liver extract (presumably containing cyanocobalamin). Yet good clinical responses were obtained with an autolysed yeast preparation (Wills, 1933) which is generally ineffective in Addisonian pernicious anæmia. It was evident, therefore, that yeast contained some unknown anti-anæmic principle (the ' Wills' factor ') that was different from the factor present in purified liver extract (cyanocobalamin).

Then an unexpected clue came from an unrelated field of biochemistry ; Mitchell *et al.* (1941) had obtained from spinach a preparation (called by them ' folic acid ') that was highly active for the growth of the micro-organism *Lactobacillus casei.* It was found that this preparation would cure an anæmia produced by dietary means in chicks. The isolation of a crystalline active principle from preparations of the '*L. casei* factor ' was announced in 1945 by a large team of American industrial chemists. The same team accomplished its synthesis in the following year. The pure synthetic substance was called pteroylglutamic acid (PGA). Its synthesis was doubtless aided by the early recognition of the fact that the most complex part of the molecule was a pterin. This group of biological compounds was known from the pioneer work of Sir Frederick Gowland Hopkins. In 1885 he had begun to investigate the pigments present in the wings of butterflies. Many years later he summarised (Hopkins, 1942) the chemical properties of the pterins extracted from them ; he recognised their chemical similarity to the purines of nucleic acid and suggested that one at least was physiologically important for mammals.

It was soon found that the pure, synthetic PGA would cure the aforementioned dietary anæmia in chicks and also in monkeys. Hence it was reasonable to try it empirically in Addisonian anæmia ; a dramatic increase in the red cell and hæmoglobin levels resulted which was comparable in degree to that produced by liver extract. However, before long it was apparent that it was no satisfactory agent for the treatment of this disease since the neurological lesions were not improved and were often made worse (Davidson & Girdwood, 1947). Some time was to elapse before it was shown that the real therapeutic role of PGA lay in the treatment of the megaloblastic anæmias of malnutrition, pregnancy and malabsorption (Chapter 36). Thus the essential correctness of Lucy Wills' original observation that there are at least two different dietary factors concerned with megaloblastosis was shown to be correct. There is still some doubt, however, whether the Wills' factor consists solely of PGA or whether some further, as yet unidentified, factor may be concerned. For review article with many references the reader is referred to Girdwood (1960).

CHEMISTRY

The chemical structure of PGA was found to be as follows :



pteroylglutamic acid

It is a yellow crystalline substance, sparingly soluble in water and stable in acid solution. When heated in neutral or alkaline media, however, it undergoes fairly rapid destruction, so that much of it is destroyed by some methods of cooking (see below). Several closely allied compounds have been identified in living matter ; pteroyltriglutamate and pteroylheptaglutamate contain three and seven glutamic acid residues respectively. They are known as the conjugated forms of the vitamin. Another naturally occurring derivative, ' citrovorum factor ' or folinic acid, has a formyl group$\text{—}\overset{O}{\overset{/\!/}{\mathrm{C}}}\text{—OH}$ or ' one-carbon unit ' attached to PGA molecule.

NOMENCLATURE

It is useful to employ the term ' folic acid ' as meaning any substance identified in natural materials having the same general biological properties as PGA, thus including the compounds mentioned above and possibly other pterin derivatives. This has the same advantage as that of retaining the term ' vitamin D ' to denote any sterol related to calciferol with similar biological activity.

PHYSIOLOGICAL ACTIVITY

The conjugated forms of the vitamin can be converted to PGA in the body by certain enzymes known as conjugases. Further, PGA is at least partly converted by the liver to folinic acid, which is therapeutically active. There is some evidence that ascorbic acid assists this conversion. Folinic acid may be the active form in which human tissues make use of the vitamin.

Naturally there has been a great deal of research and even more speculation about the precise metabolic role of folic acid in promoting the formation of red blood cells. The chemical configuration of the pterins and their close resemblance to the purines suggests some association with nucleic acid metabolism. The addition of the formyl group that takes place in the conversion of PGA to folinic acid indicates a role in the transfer of one-carbon units within the cell. One-carbon units are required in the synthesis of amino acids, the purine ring and thymidine. As yet, however, there is no precise definition of the physiological action of the vitamin. Experimental deficiency of folic acid in human volunteers has not yet been achieved.

Laboratory Diagnosis

Folic acid may be estimated in fluids by making use of its growth-promoting properties for a variety of micro-organisms. Such methods are laborious and time-consuming ; nevertheless the ' folic acid absorption test ' (Girdwood, 1953) has proved of value, especially in doubtful cases of malabsorption syndrome. A recent test for folic acid deficiency depends on the measurement of formiminoglutamic acid in the urine (Spray & Witts, 1959). This substance is an intermediary in the breakdown of histidine. Normally the formimino group is transferred to a derivative of PGA. In patients with folic acid deficiency, it appears to be excreted attached to glutamic acid. In patients with a megaloblastic anæmia due to folic acid deficiency, large amounts of formiminoglutamic acid are excreted after a test dose of histidine.

Dietary Sources

Fresh, dark-green vegetables and liver are the best sources, with other green vegetables, cauliflower and kidney the next best. Beef, fresh fruits, root vegetables and wheaten flour contain a little, whilst milk, eggs and poultry are poor in folic acid. Considerable losses may occur in the process of cooking. An average British diet contains perhaps 100 μg. daily before cooking and about 50 μg. when served.

Recommended Allowances

It is not yet possible to give any definite figure for a satisfactory intake of folic acid. Patients with megaloblastic anæmia need 1 mg. or more daily to produce an optimal hæmatological response. Such amounts are certainly considerably in excess of the needs of normal people who excrete more folic acid when their daily intake exceeds 200 μg. The amount of folic acid present in the diets of healthy people suggests that a daily intake of the order of 50 μg. is ordinarily quite sufficient.

THERAPEUTIC USES

Pteroylglutamic acid is useful in the treatment of nutritional megaloblastic anæmia, the megaloblastic anæmias of pregnancy and infancy, and in some cases of the malabsorption syndrome. A daily dose of 5 to 10 mg. by mouth is usually sufficient. It should never be used in Addisonian anæmia because it does not prevent or cure the neurological features of that disease.

TOXICITY

It does not appear that PGA causes any toxic effects in the doses ordinarily employed. However, certain synthetic analogues of PGA are highly poisonous, notably aminopterin which has been used as a cellular poison in the treatment of leukæmia.

VITAMIN B_6—PYRIDOXINE AND RELATED COMPOUNDS

HISTORY

The vitamin was first identified as the factor in the vitamin B complex—distinct from thiamine and riboflavin—that would cure a specific type of nutritional dermatitis in rats. Birch and Gyorgyi (1936) first concentrated the vitamin in 1936; two years later it was isolated by five independent groups of workers. By 1939 three different laboratories had achieved the synthesis of pyridoxine.

CHEMISTRY

Vitamin B_6 is not a single substance but consists of three closely related chemical compounds, pyridoxine, pyridoxal and pyradoxamine of pyridoxine with similar physiological actions. The chemical structure is given on page 135.

PHYSIOLOGICAL ACTION

Pyridoxal phosphate is the coenzyme or prosthetic group of the enzyme *transaminase* which plays a decisive part in the metabolism of the amino acids as described in Chapter 9.

Vitamin B_6 deficiency has been produced by dietary means in several species of animals including monkeys, dogs, pigs, rats and chickens. In rats the typical dermatitis has been unfortunately called ‘ acrodynia ’ since it has nothing in common with the human disease of that name (*alias* Pink disease). The livers of pyridoxine-deficient rats contain more fat than normal. Pigs developed a microcytic hypochromic anæmia and a peripheral neuropathy; dogs developed epileptiform convulsions, whereas monkeys were found to have atheromatous changes in the arteries.

HUMAN DEFICIENCY

It is now well established (Tower, 1956) that pyridoxine has a role in the metabolism of nervous tissue. Pyridoxine deficiency occurs in infants, though it is *very rare* ; it is characterised by increased irritability and convulsions. The symptoms are promptly relieved by pyridoxine in adequate amounts (10 mg. or more daily). Normal infants require much less, and the cause of the deficiency is unknown. Scriver (1960), who describes in detail one case in which a number of biochemical studies were made, speculates that it is another inborn error of metabolism.

Several authors (Dawson *et al.*, 1961 ; Havard, 1961) have described patients with hypochromic anæmia refractory to iron therapy who responded dramatically to pyridoxine. High levels of serum iron indicated no iron deficiency. These patients were probably not suffering from a dietary lack of the vitamin but from some defect in its intermediary metabolism. This condition is also very rare.

There are many reports of signs and symptoms such as insomnia, weakness, cheilosis, stomatitis and dermatitis disappearing after treatment with pyridoxine. Many of the patients had been on poor diets and pyridoxine deficiency may well have been in part responsible for these features. There are, however, no clear-cut signs characteristic of pyridoxine deficiency. All the above signs, and in addition a peripheral neuropathy, have been produced by deoxypyridoxine, which acts as an antagonist of the vitamin. The peripheral neuritis, which may develop after isoniazid therapy for tuberculosis, is also believed to be a conditioned pyridoxine deficiency.

Pyridoxine is needed for the normal metabolism of tryptophan to nicotinic acid ; in the absence of an adequate supply of the vitamin, tryptophan is converted to an abnormal metabolite, xanthurenic acid. The urinary excretion of xanthurenic acid before and after a test dose of tryptophan has been used as a test of the state of pyridoxine nutrition. Theron *et al.* (1961) found that judged by this criterion there was evidence of pyridoxine lack in 4 out of 18 children with kwashiorkor. None of these patients had any distinctive clinical features other than those usually encountered in kwashiorkor.

DIETARY SOURCES

Vitamin B_6 can be measured in foodstuffs by assay on rats or chicks, by its growth-promoting properties for certain micro-organisms, or by various chemical methods. The results obtained by these different methods do not always agree and as yet it is not possible to give more than a general idea of the dietary sources of the vitamin. It seems to be very widely distributed both in plant and animal tissues, and more uniformly than most other components of the B complex, which perhaps reflects its importance in the metabolism of every kind of cell. Meat, liver, vegetables and the outer coats (bran) of cereal grains are all good sources.

Recommended Allowances

Infants are said to need about 0·2 to 0·3 mg. daily. No figure can be given for adults, but most human diets provide about 1 to 2 mg. daily.

Therapeutic Uses

In iron-resistant hypochromic anæmia due to pyridoxine deficiency, doses up to 100 mg. daily have been used. When a primary dietary deficiency is suspected in an adult, a daily dose of 10 mg. may be tried.

Toxicity

No untoward reactions have been reported from the administration of pyridoxine to human subjects, but a synthetic analogue—desoxypyridoxine—is highly poisonous.

PANTOTHENIC ACID

Introduction

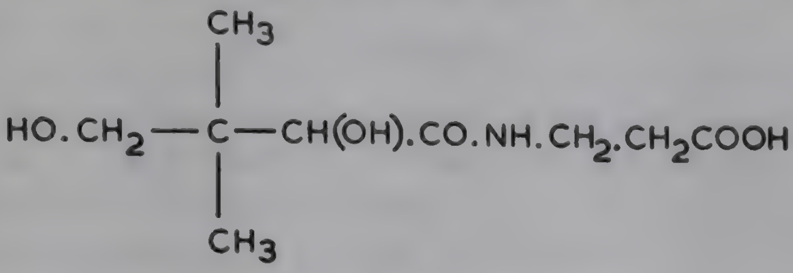
Pantothenic acid is a constituent of coenzyme A and present in all living matter ; its distribution in natural foodstuffs is so widespread that deficiency of the vitamin is unlikely to occur in man except perhaps when processed foods form a large proportion of the diet.

History

After the discovery of riboflavin, nicotinic acid and pyridoxine it was soon realised that there was still at least one other factor left in materials containing the hypothetical ' vitamin B_2.' This ' filtrate factor ' was first recognised by its ability to prevent a specific type of dermatitis that develops round the eyes and beak of chicks fed on a diet deficient in it, and by its ability to prevent grey hair in black rats similarly fed. Attempts to isolate this factor were proceeding along orthodox lines, using rats and chicks as the test animals when, as in the case of folic acid, the microbiological approach unexpectedly revealed the vitamin. R. J. Williams (1939) first isolated the vitamin, using the growth of yeast as a test of its presence and later achieved its synthesis. He called it pantothenic acid because of its apparently universal distribution in living matter.

CHEMISTRY

Pantothenic acid consists of a di-methyl derivative of butyric acid joined by a peptide linkage to the amino acid β-alanine. The vitamin itself is a pale yellow oily liquid that has never yet been crystallised, but its calcium salt crystallises readily and this is the form in which it is generally available. Though stable in neutral solution, the vitamin is easily destroyed by heat, both on the acid and alkaline side of neutrality. In fact its lability to heat links it more closely with the ' heat-labile vitamin B_1' than with the ' heat-stable vitamin B_2.'



$$HO.CH_2-\underset{\substack{|\\ CH_3}}{\overset{\substack{CH_3\\ |}}{C}}-CH(OH).CO.NH.CH_2.CH_2COOH$$

pantothenic acid

PHYSIOLOGICAL ACTION

The essential physiological action of pantothenic acid as part of the coenzyme A molecule is described in Chapter 9.

Deficiency in animals

Lack of pantothenic acid in the diet of rats produces a failure of growth, greying of the hair, an accumulation of porphyrin on the whiskers round the nose and, of especial interest, hæmorrhage and necrosis in the adrenal glands. Some rats develop a fatal aplasia of the bone marrow, with anæmia and leucopenia. In chicks, apart from the typical dermatitis, there is a neuropathy characterised by myelin degeneration of the tracts in the spinal cord. Dogs deficient in the vitamin develop fatty livers. In pigs there is a peripheral neuropathy affecting the sensory nerves.

HUMAN DEFICIENCY

In view of the wide distribution of pantothenic acid in foodstuffs it is not surprising that human deficiency of the vitamin has not been definitely described ; several workers have reported that the vitamin relieves the symptoms of the burning feet syndrome (p. 445), but this condition is certainly not due to deficiency solely of pantothenic acid.

DIETARY SOURCES

Pantothenic acid is found universally in all living matter. The best sources are liver, kidney, yeast, egg yolk and fresh vegetables. In most cooking and baking procedures there is little loss of the vitamin, but temperatures above boiling point may cause considerable loss. Frozen meat may lose much of its original content in the drip that occurs with thawing.

THERAPEUTIC USES

So far there is no clearly defined use for synthetic pantothenic acid, though it may be tried, in doses of 10 mg. daily of the calcium salt by intramuscular injection, in patients suffering from the burning feet syndrome (p. 445). It will not prevent the development of grey hair in man.

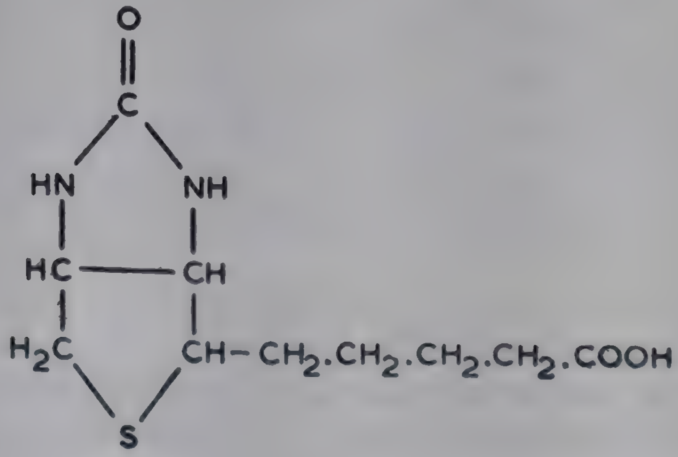
BIOTIN

INTRODUCTION

Biotin deficiency does not occur in man except under extraordinary circumstances, yet it is a vitamin of such physiological interest that it merits some mention.

HISTORY

Rats fed on the raw whites of eggs as their sole source of animal protein develop a dermatitis and become emaciated. Raw egg-white contains a particular protein (avidin) which combines with biotin rendering it unavailable to the rat. By cooking the eggs the avidin is denatured and the biotin liberated. The vitamin was finally synthesised in 1943 and proved to have the following formula :



biotin

PHYSIOLOGICAL ACTION

Biotin is one of the most active biological substances known ; extremely small amounts have marked effects on the growth of yeast and certain bacteria. This provides the means by which it can be measured in foodstuffs. In living matter it is mostly bound to protein, probably as the prosthetic group of several enzymes. It has been reported to be capable of catalysing several important biochemical reactions.

DEFICIENCY IN MAN

Sydenstricker and his colleagues (1942) produced experimental biotin deficiency by feeding four volunteers on a diet very poor in all the vitamins of the B group except riboflavin. This diet was largely composed of dried egg-white which supplied 30 per cent. of the calories in the diet. Other known components of the B complex were added in synthetic form. After 10 weeks on the diet the subjects were fatigued, depressed and sleepy, with nausea and loss of appetite. Muscular pains, hyperæsthesiæ and paræsthesiæ developed, without reflex changes or other objective signs of neuropathy. As the authors point out, these features could not be distinguished from those previously attributed to thiamine deficiency. The tongue became pale with loss of papillæ. The skin became dry, ' crackled,' with fine branny desquamation (Chapter 37) and anæmia developed. All of these signs and symptoms were relieved by the injection of a concentrated preparation containing 150 to 300 μg. of biotin daily. The authors concluded : " The phenomena observed were similar to some of those observed in spontaneous avitaminoses." The proper conclusion from this observation is that any sudden or serious derangement in the enzyme systems of the body, such as occur as a result of acute deprivation of biotin or thiamine, may produce similar clinical changes.

The only clinical case of biotin deficiency thus far described in man is that of an eccentric patient who lived for some time on a diet consisting mainly of six dozen raw eggs weekly, washed down by 4 quarts of red wine daily (Williams, 1943). He had a severe dermatitis which responded to injections of the methyl ester of biotin.

DIETARY SOURCES

Yeasts and bacteria of many species either make or retain biotin ; it seems probable that man, if indeed he cannot make the vitamin in his tissues, can obtain all he needs of this most potent nutrient from the numerous benign micro-organisms that are present in his daily food or inhabit his large intestine. Moreover, biotin is present in a variety of bacteria-free foods. Liver, kidney and yeast extract are good sources. Pulses, nuts, chocolate and some vegetables (*e.g.* cauliflower) are fair sources. By contrast other animal meats, dairy produce and cereals are relatively poor.

ALLOWANCES AND THERAPEUTIC USES

The human body probably utilises a few micrograms of biotin daily. It is very doubtful whether this needs to be included in the diet. Obviously the only use for biotin in the relief of dietary errors is for people who have eaten too many raw eggs. There is no justification for the inclusion of synthetic biotin in multivitamin capsules.

OTHER COMPONENTS OF THE VITAMIN B COMPLEX

Para-aminobenzoic acid.—This compound, originally identified as a growth factor for many species of bacteria, has been reported to be a necessary nutrient for the rat and the chick, perhaps because it forms a part of the molecule of pteroylglutamic acid (PGA). There is no evidence that it is a necessary vitamin for man. Notwithstanding this it has been tried empirically in a considerable number of diseases, but without any clear proof of its value except possibly in the case of rickettsial infections. In the latter its use has now been superseded by chloramphenicol and aureomycin.

Inositol.—This was first identified as a growth factor for yeasts and moulds, though not for bacteria. It is a necessary dietary factor for mice and rats. Chemically, inositol is interesting because its hexaphosphate ester is *phytic acid* (p. 158). Its very wide distribution in foods, both of vegetable and animal origin, makes it very unlikely that human deficiency of inositol ever occurs. Nevertheless its presence in all actively metabolising tissues suggests that it is a physiologically active substance. It is found in the phospholipids of the tissues and, since inositol deficiency in rats can cause a fatty liver (Macfarland & McHenry, 1948), it is evidently one of the lipotropic factors.

Choline.—This is sometimes classed with the vitamins of the B group, but is better discussed in connection with physiology of the liver (Chapter 39).

CHAPTER 15

RECOMMENDED ALLOWANCES OF NUTRIENTS

NUMEROUS tables setting forth standards of dietary needs have been prepared by various official bodies and by individual nutritionists in the last 25 years. Tables 15, 1 and 15, 2 record those of the British Medical Association and of the National Research Council of the U.S.A. Frequent reference to both will be found in current medical literature. The differences between them are not great and we would subscribe to either with minor reservations.

Much of the evidence on which these tables have been based has been reviewed in the previous chapters. It is important to understand the aims, uses and limitations of these tables. The allowances which they recommend are intended for large groups of people and are not applicable to individuals. Any particular individual's need may differ markedly from the figures set out. The evidence that there are wide variations between individual people for individual nutrients has been ably reviewed by Williams (1956). The amounts of each nutrient as recommended in these tables should be sufficient not merely to prevent deficiency diseases but also to sustain a vigorous and healthy life. For this latter purpose a liberal margin of safety has been allowed.

It is important to realise that the tables are national allowances and are related to the customary diets of the people of the countries concerned. They are not necessarily suitable for export. In particular they are not applicable to underdeveloped countries. The figures, translated into foodstuffs, represent diets which have little or no relation to the diets consumed in many parts of Asia, Africa and Latin America. In such areas the use of these tables would be quite unrealistic. They would set a standard that is beyond the reach of practical possibilities. The Indian Research Fund Association has set out a table of allowances for use in India (Table 15, 3). These allowances are a compromise between estimates of physiological need and agricultural possibilities. They are practical aims which, if reached, would result in an immense improvement in the nutrition of the people, though their diets might still not be ideal.

The drawing up of a suitable set of national allowances is an essential part of any practical national food policy. In any country such allowances would naturally require revision at regular intervals. For instance the increasing mechanisation of industry and the sedentary nature of the work of so many people to-day make it not unlikely that both the British and American tables overestimate the total caloric needs of each country.

Standards have two main uses. First, they provide a yardstick against

TABLE 15, 1. *Summary of daily allowances as recommended by the Nutrition Committee of the British Medical Association* (1950)

(All values per day)

Age and sex	Requirement class *	Calories	Protein	Calcium	Iron	Vitamin A and Carotene	Vitamin D	Thiamine	Niacin	Riboflavin	Ascorbic acid	Iodine
Both sexes—			g.	g.	mg.	i.u.	i.u.	mg.	mg.	mg.	mg.	µg.
0–1 year . .	...	1000	37	1·0	6·5	3000	800	0·4	4	0·6	10	...
2–6 years .	...	1500	56	1·0	7·5	3000	400	0·6	6	0·9	15	150
7–10 years .	...	2000	74	1·0	10·5	3000	400	0·8	8	1·2	20	150
11–14 years .	...	2750	102	1·3	13·5	3000	400	1·1	11	1·6	30	150
Males—												
15–19 years .	...	3500	130	1·4	15·0	5000	400	1·4	14	2·1	30	150
20 years and over	0	1750	51	0·8	12·0	5000	...	0·7	7	1·0	20	100
	1	2250	66	0·8	12·0	5000	...	0·9	9	1·4	20	100
	2	2750	80	0·8	12·0	5000	...	1·1	11	1·6	20	100
	3	3000	87	0·8	12·0	5000	...	1·2	12	1·8	20	100
	4	3500	102	0·8	12·0	5000	...	1·4	14	2·1	20	100
	5	4250	124	0·8	12·0	5000	...	1·7	17	2·6	20	100
	6	5000	146	0·8	12·0	5000	...	2·0	20	3·0	20	100
Females—												
15–19 years .	...	2500	93	1·1	15·0	5000	400	1·0	10	1·5	30	150
20 years and over	0	1500	44	0·8	12·0	5000	...	0·6	6	0·9	20	100
	1	2000	58	0·8	12·0	5000	...	0·8	8	1·2	20	100
	2	2250	66	0·8	12·0	5000	...	0·9	9	1·4	20	100
	3	2500	73	0·8	12·0	5000	...	1·0	10	1·5	20	100
	4	3000	87	0·8	12·0	5000	...	1·2	12	1·8	20	100
	5	3750	109	0·8	12·0	5000	...	1·5	15	2·2	20	100
Pregnancy—												
First half .	...	2500	93	0·8	12·0	6000	400	1·0	10	1·5	40	150
Second half .	...	2750	102	1·5	15·0	6000	600	1·1	11	1·6	40	150
Lactation . .	...	3000	111	2·0	15·0	8000	800	1·4	14	2·1	50	150

* REQUIREMENT CLASSES

0—No work, lying in bed.
1—Sedentary work.
2—Light work.
3—Medium work.
4—Heavy work.
5—Very heavy work.
6—Extremely heavy work.

TABLE 15, 2. *Food and Nutrition Board, National Research Council recommended daily dietary allowances,* revised* 1953

Designed for the maintenance of good nutrition of healthy persons in the U.S.A.

(Allowances are considered to apply to persons normally vigorous and living in temperate climate)

	Weight	Height	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin	Ascorbic Acid	Vitamin D
Men—	kg. (lb.)	cm. (in.)		gm.	gm.	mg.	i.u.	mg.	mg.	mg.	mg.	i.u.
25 years	65 (143)	170 (67)	3200†	65	0·8	12	5000	1·6	1·6	16	75	...
45 years	65 (143)	170 (67)	2900	65	0·8	12	5000	1·5	1·6	15	75	...
65 years	65 (143)	170 (67)	2600	65	0·8	12	5000	1·3	1·6	13	75	...
Women—												
25 years	55 (121)	157 (62)	2300†	55	0·8	12	5000	1·2	1·4	12	70	...
45 years	55 (121)	157 (62)	2100	55	0·8	12	5000	1·1	1·4	11	70	...
65 years	55 (121)	157 (62)	1800	55	0·8	12	5000	1·0	1·4	10	70	...
Pregnant (third trimester)	...	...	Add 400	80	1·5	15	6000	1·5	2·0	15	100	400
Lactating (850 ml. daily)	...	...	Add 1000	100	2·0	15	8000	1·5	2·5	15	150	400
Infants ‡—												
0–1 month §	...	...	...	...	...	...	...	...	...	...	...	...
1–3 months	6 (13)	60 (24)	120/kg.	3·5/kg.‡	0·6	6	1500	0·3	0·4	3	30	400
4–9 months	9 (20)	70 (28)	110/kg.	3·5/kg.‡	0·8	6	1500	0·4	0·7	4	30	400
10–12 months	10 (22)	75 (30)	100/kg.	3·5/kg.‡	1·0	6	1500	0·5	0·9	5	30	400
Children—												
1–3 years	12 (27)	87 (34)	1200	40	1·0	7	2000	0·6	1·0	6	35	400
4–6 years	18 (40)	109 (43)	1600	50	1·0	8	2500	0·8	1·2	8	50	400
7–9 years	27 (59)	129 (51)	2000	60	1·0	10	3500	1·0	1·5	10	60	400
Boys—												
10–12 years	35 (78)	144 (57)	2500	70	1·2	12	4500	1·3	1·8	13	75	400
13–15 years	49 (108)	163 (64)	3200	85	1·4	15	5000	1·6	2·1	16	90	400
16–20 years	63 (139)	175 (69)	3800	100	1·4	15	5000	1·9	2·5	19	100	400
Girls—												
10–12 years	36 (79)	144 (57)	2300	70	1·2	12	4500	1·2	1·8	12	75	400
13–15 years	49 (108)	160 (63)	2500	80	1·3	15	5000	1·3	2·0	13	80	400
16–20 years	54 (120)	162 (64)	2400	75	1·3	15	5000	1·2	1·9	12	80	400

* In planning practical dietaries, the recommended allowances can be attained with a variety of common foods which will also provide other nutrient requirements less well known; the allowance levels are considered to cover individual variations among normal persons as they live in the United States subjected to ordinary environmental stresses.

† These calorie recommendations apply to the degree of activity for the reference man and woman described on page 27 of the text. For the urban "white-collar" worker they are probably excessive. In any case, the calorie allowance must be adjusted to the actual needs of the individual as required to achieve and maintain his desirable weight.

‡ The recommendations for infants pertain to nutrients derived primarily from cow's milk. If the milk from which the protein is derived is human milk or has been treated to render it more digestible, the allowance may be in the range of 2 to 3 gm./kg. There should be no question that human milk is a desirable source of nutrients for infants even though it may not provide the levels recommended for certain nutrients.

§ During the first month of life, desirable allowances for many nutrients are dependent upon maturation of excretory and endocrine functions. Therefore no specific recommendations are given.

TABLE 15, 3. *Daily allowances recommended by the Nutrition Advisory Committee, Indian Medical Research Council, revised by Patwardhan* (1960)

(All values per day)

	Calories	Protein	Calcium	Iron	Vitamin A	Vitamin D	Thiamine	Ascorbic acid
Man (55 kg., 120 lb.)—		g.	g.	mg.	i.u.	i.u.	mg.	mg.
Light or sedentary work	2400	55			3000–4000			50
Moderate work	2800							
Very hard work	3900		1·0	20–30			1·0–2·0	
Woman (45 kg., 100 lb.)—								
Light or sedentary work	2000	45						
Moderate work	2300							
Very hard work	3000		...					
Pregnancy (later half)	2300	100	1·5			400–800		
Lactation	2700	110	2·0					
Children—								
0–6 months	120/kg.	3.5/kg.	1·0–1·5	10–30	3000–4000	400–800	0·5–1·0	30–50 and over
7–12 months	100/kg.							
1–3 years	1200							
4–6 years	1500							
7–9 years	1800	3·0/kg.						
10–12 years	2100	2·5/kg.						
13–15 years :								
Girls	2100							
Boys	2500							
Adolescents—								
16–19 *years :*								
Girls	2100	2·0/kg.						
Boys	3150							

N.B.—The estimates of the protein requirements are subject to the proviso that dietary protein is derived from more than one foodstuff.

which the diets of different sections of a community or a particular socio-economic class can be measured. Thus in Britain the National Food Survey, in its annual reports, records how the diets of different classes of people measure up to the allowances for different nutrients as recommended by the B.M.A. Committee. Thus vulnerable points in the British dietary can readily be detected. Secondly, standards are necessary for any planned agricultural policy and an organised food trade. In most countries the government exerts some direct or indirect control over both the quantity and quality of food grown by farmers and also over international food trade. If this control is to be adjusted to the physiological needs of the people, some assessment of their total food requirements is necessary. Such an assessment can only be obtained through the use of standard tables of recommended allowances.

PART II—FOOD

CHAPTER 16

THE USE OF FOOD TABLES

IN Part I the physiology of the human body was considered from the point of view of the nutritionist interested in its needs for nutrients. These nutrients were described, as far as possible, in chemical terms; the amounts of each which must be supplied in the diet in order to prevent disease, maintain health and allow full physical activity were discussed. In Part II an attempt is now made to describe the most important foods of man and the manner in which they combine to supply these essential nutrients in various national diets. The main concern will be with the chemical properties of the food, though psychological and sociological aspects of food are also introduced where relevant.

A vast number of analyses have been carried out on the chemical composition of foods and many hundreds of papers on the subject have been published. Some of these deal with only a small number of foods or a single nutrient. There are, however, several large compilations which have been widely used and can be recommended. Well-known tables recording food analyses are given, for British foods by McCance and Widdowson (1960), for American foods by Watt and Merrill (1950), for Indian foods by Aykroyd (1951), for tropical foods by Platt (1962), and a general compilation for international use by Chatfield (1949, 1954).

Every dietitian and nutritionist should be in possession of one of these or some other suitable table of food values, for it is these tables that enable dietetics to be a science as well as an art. But it is important to consider the information that such tables can provide, and especially to be able to assess their reliability and degree of accuracy. In order to understand how to use tables correctly it is important to read the introductions which describe *how* the tables have been compiled. If this is not done the tables may be abused by improper application. Widdowson and McCance (1943) have aptly stated the position thus: " There are two schools of thought about food tables. One tends to regard the figures in them as having the accuracy of atomic weight determinations; the other dismisses them as valueless on the grounds that a foodstuff may be so modified by the soil, the season or its rate of growth that no figure can be a reliable guide to its composition. The truth, of course, lies somewhere between these points of view."

The uses to which food tables may be applied are now described before discussing their limitations, accuracy and reliability.

Clinical practice.—Accurate prescribing of diets containing known amounts of some of the important nutrients is essential for the treatment

of certain diseases. Diets low in calories for obese patients, diets containing known amounts of protein, carbohydrate and fat for diabetics, diets rich in protein for convalescents, and diets with a low sodium content for patients with congestive heart failure are well-known examples.

Accurate interpretation of a dietary history may be a valuable aid to diagnosis. For example, an estimate of the amount of ascorbic acid in a patient's previous diet may assist in deciding whether a purpuric rash is a manifestation of scurvy or of some blood disease. An estimate of the amount of thiamine in a patient's usual diet may help to determine whether œdema and heart failure can be attributed to beriberi or to some other cardiac disorder. Many problems of this nature arise in clinical medicine.

Public health practice.—Once the diet consumed by a large population group has been assessed by a dietary survey, it may then become important to know whether the intake of each of the principal nutrients is sufficient to prevent the likelihood of the appearance of any of the deficiency diseases. It may also be necessary to decide whether the caloric intake will supply the energy required for physical work without drawing on body reserves of fat with consequent loss of weight. How far the food consumption of a nation measures up to the standards of recommended allowances, described in Chapter 15, is another problem requiring careful consideration.

In prescribing diets for closed communities such as the armed services, convalescent homes, boarding schools, old people's homes, prisons, etc., it is important to make sure that any recommended ration scale is compared with acceptable standards and that its use is not likely to cause deficiency disease.

Clinical research.—Accurate knowledge of the intake of essential nutrients both of patients and normal subjects is often necessary in investigating metabolic problems both in health and disease.

LIMITATIONS

How far can food tables help to provide answers to the practical problems discussed above ? There is the drawback that each figure in the table can only be an average of the analyses of a limited number of samples of each food. Thus there will be variations in the chemical composition of different samples of the potatoes grown on Mr Gunn's potato patch in the Orkney Islands. But there will be much larger variations between the chemical composition of these potatoes and of those grown in a garden in New England, on the altiplano in Peru or a field in Connemara. For this reason it is best to use tables based on analyses of local foods. A few principles can be set out which will help to appreciate the significance of these variations and so allow an intelligent use of the tables.

Water.—Perhaps the most variable chemical constituent of foods is water. Thus figures for the composition of foods containing large amounts of water are always uncertain. Cereal grains contain relatively little water and, although there are variations in the nutrient content of different varieties of the same cereal, these are relatively small. Cereals have been extensively analysed and tables give reliable figures for most of them. Diets with a high cereal content are usually associated with poverty. Thus the error involved in calculating the nutrients consumed by poor people, such as a Bantu mechanic in Johannesburg living largely on maize and sorghum, will be much less than the error involved in making a similar calculation for a rich business executive in Chicago with his varied diet.

Proximate principles.—Perhaps the least variable of the chemical constituents of foods is protein. On numerous occasions when the protein content of a diet has been calculated from tables and simultaneously determined by analyses of aliquot portions of the diet, there has been very good agreement. The error in using tables to calculate the protein content of a diet is not likely to be more than 7 per cent.

The error in estimating carbohydrate and fat from the tables is also not very great—with one important exception. This is the calculation for meat. There are large variations in the fat content of different helpings of beef, mutton or pork. These variations will greatly affect the calculated caloric value of the meat.

Calories.—The caloric value of a diet can usually be calculated with an accuracy sufficient for practical purposes. The error introduced by the use of tables should not be more than 10 per cent. (250 Cal. in a 2500 Cal. diet) unless the diet contains large quantities of meat. Thus estimates of most diets can be made with the help of the tables, which suffice for most clinical and public health purposes. The tables have certainly a sufficient degree of accuracy to justify their customary use in prescribing for obese and diabetic patients. The error will be minimal in assessing simple diets based on cereals and at a maximum with rich mixed diets. Errors of up to 10 per cent. are too great for most metabolic studies and tables of food analyses are of little use to clinical scientists and physiologists, who must make their own analyses on aliquot samples of their subjects' diets.

Vitamins.—The variations in the vitamin content of foods is very much greater than the variations in proximate principles. They are especially large in all classes of vegetables and fruits and particularly for vitamin A activity and ascorbic acid content. These variations are so great that the use of tables to give a quantitative assessment of the vitamin content of a diet may produce a set of figures that have no factual basis. With poor diets containing only small amounts of foods rich in vitamins, the errors will be less. For instance food tables should enable a statement to be made as to whether a diet contains less or more than 5 mg. of ascorbic acid, *i.e.* whether or not it is likely to be associated with scurvy. Similar assessments can be made for vitamin A activity and the principal vitamins of the B group. In this way food tables can help in deciding whether a given diet is likely to give rise to a major vitamin deficiency disease or not. This, of course, is a very practical aid in both clinical and public health work.

Minerals.—For minerals the tables are of limited value. There are enormous variations in the iron content of different samples of the same food. Different tables can give very different values for the iron content of a diet (Ranganathan, 1938). For calcium the problem is complicated by the lack of precise knowledge of how much of the calcium in foods can be absorbed. In many foods rich in calcium, the calcium is physiologically only partially available. Tables as at present constituted cannot overcome this difficulty. For the other minerals systematic analyses of food have only been carried out on a small scale. In short, food tables are of little use in calculating the mineral content of diets.

COMMENT

Thus food tables are practical and well-tried guides to many important nutritional problems, but they can be used (and often have been) to produce figures which are meaningless. It is important that the student realises their limitations.

For those who wish to study this problem more fully there is a useful paper by Woolf (1954) who gives simple mathematical treatments of some of the points on which we have touched. Youmans and his colleagues (Kaiser *et al.* 1947) in the U.S.A., and McHenry and his colleagues (Patterson & McHenry, 1941 ; Young & McHenry, 1942, 1943) in Canada have published helpful records of diets in which the contents of nutrients determined by chemical analysis and calculated from tables are compared.

As already stated we recommend all students to acquire one or other of the food tables of repute.

Chapter 17

CEREALS

CEREAL grains are the seeds of domesticated grasses. Stable civilisations have arisen only when primitive hunting communities have learned how to raise successive cereal crops from cultivated land. Without the use of cereals man is reduced to an uncertain and unsettled nomadic life. They have been modified and improved by centuries of cultivation and selective breeding.

In many rural areas, including large parts of Asia and Africa, cereals provide more than 70 per cent. of the calories in the common diet. In more highly developed countries their contribution is less, but even in the U.S.A. and Great Britain cereals remain the most important single food and provide about 25 per cent. of the calories. Only isolated people, such as the Eskimoes and a few pastoral tribes, are almost entirely carnivorous and, having never reached a high level of civilisation, do not cultivate cereals or root crops.

The principal cereals are wheat, rice, maize, millets, oats and rye. The name ' corn ' is generally used in the English-speaking world to mean the most familiar local cereal—whatever the species. Thus ' corn ' in Scotland means oats, in England, wheat, and in the U.S.A., maize. The choice depends largely on climate and economic factors, but custom and precedent are also important. All cereals can be ground into flour for cakes or porridge, but only wheat and rye will bake into bread. Wheat is now the cereal of choice in temperate or dry climates in most parts of the world. It is extensively grown in the U.S.A., Canada, Argentine, Australia, Europe, Russia, Egypt and Northern India.

Rice is the cereal of choice for most damp tropical climates. It grows best in the deltas of the great rivers of the tropics, since it is essentially a mud plant requiring an abundant water supply.

Maize is widely grown in the Southern States of the U.S.A., Italy, Yugoslavia, Egypt, other parts of Africa and in some regions of India. It is essentially a poor man's food, having the merit of being hardy and easily cultivated.

Millets will grow in hot climates, on poor soil with limited water supply. They are the principal crops in many dry areas in the tropics.

Oats are a hardy crop and at one time the staple food of the people of Scotland, but now are grown chiefly for cattle fodder.

Barley is mainly used for brewing, but is also eaten by man and cattle.

Rye will grow on very poor soil in cold climates and is still sown in

Scandinavia, Russia and parts of Germany. In the last five hundred years it has been progressively replaced by wheat.

The whole grains of all cereals have a similar chemical constitution and nutritive value. They provide calories and also some protein, which is usually of good biological value. They contain appreciable amounts of calcium and iron, but the value of these minerals is partly discounted by the presence of phytic acid which may interfere with their absorption. Whole cereals are totally devoid of ascorbic acid and practically devoid of vitamin A activity. Yellow maize is the only cereal containing significant amounts of carotene. Whole cereal grains also contain useful amounts of the water-soluble B group of vitamins.

TABLE 17, 1. *Nutritive value of the main whole cereal grains*

(Values per 100 g.)

	Calories	Protein	Fat	Calcium	Iron	Thiamine	Nicotinic acid	Riboflavin	Vitamin A	Ascorbic acid
		g.	g.	mg.	mg.	mg.	mg.	mg.	i.u.	mg.
Wheat (whole meal)	334	12·2	2·3	30	3·5	0·40	5·0	0·17	Trace	0
Rice (husked)	357	7·5	1·8	15	2·8	0·25	4·0	0·12	Trace	0
Maize (whole meal)	356	9·5	4·3	12	5·0	0·33	1·5	0·13	0–400	0
Millet (Sorghum)	343	10·1	3·3	30	6·2	0·40	3·5	0·12	Trace	0
Oats (rolled)	385	13·0	7·5	60	3·8	0·50	1·3	0·14	Trace	0
Rye	319	11·0	1·9	50	3·5	0·27	1·2	0·10	Trace	0

Table 17, 1 shows how similar are the nutritive values of the whole grains of all the principal cereals. To make a balanced diet, cereals must be supplemented by animal proteins, minerals and vitamins A and C. These are provided by meat, milk and fresh green vegetables. When cereal grains are consumed in their entirety an adequate supply of the B group of vitamins is ensured. If, however, the grains are first milled and outer portions of the seed, including the germ and scutellum (p. 264), discarded, there is a grave risk that there will be an insufficiency of the B group of vitamins. Fortunately oats, barley, millets and rye are usually only lightly husked and most of the whole grain is eaten. Wheat and rice, however, are invariably subjected to some degree of milling. The extent to which the milling process removes the vitamins is of the utmost importance and is considered in some detail later in this chapter. For a proper understanding of the nutritive value of the cereals and of the changes they undergo in preparing them as food for man it is necessary to consider the structure of the cereal grain and the composition of its parts.

WHEAT

Anatomy of the grain

The grain is a seed with the structure shown in Fig. 17, 1. The outer coverings are the pericarp and testa which are hard, and contain much indigestible fibre. Beneath them is the aleurone layer, which is an envelope of cells rich in protein. These outer layers form about 12 per cent. of the weight of the grain. Inside is the endosperm, comprising about 85 per cent. of the weight of the grain, and consisting of an inner and outer portion. The germ (or embryo)—situated at the lower end of the grain—consists of the plumule and root. The embryo is attached to the grain by a special structure, the scutellum. The embryo and scutellum are only just visible to the naked eye and form about 3 per cent. of the total weight of the grain.

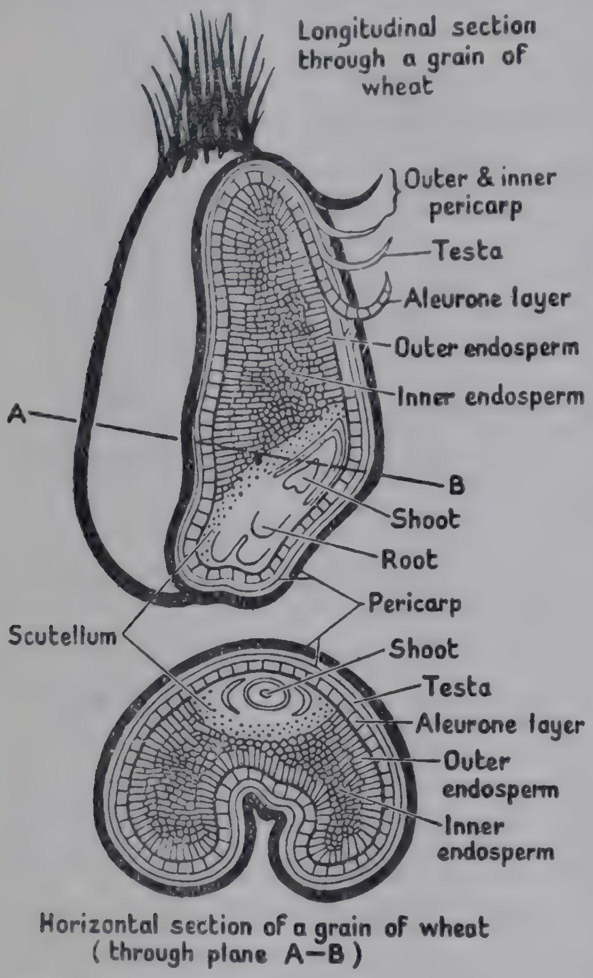


FIG. 17, 1. Structure of the wheat grain. (From McCance, 1946).

Distribution of nutrients in the grain

This is not uniform. The germ is relatively rich in protein and the B group of vitamins. So also is the scutellum, which contains about fifty times more thiamine than the whole grain. Thus an important part, perhaps as much as half of the total thiamine in the grain, may be present in the scutellum. The outer layers of the endosperm and the aleurone layer contain a higher concentration of protein, vitamins (especially nicotinic acid) and phytic acid than the inner endosperm. The inner endosperm contains most of the starch and protein in the grain, though the protein is at a slightly lower concentration than in the outer layers and germ.

Distribution of nutrients in flour

Wheat is usually ground into flour before being prepared as food. Flour containing the whole grain may be used but usually the germ and a varying proportion of the outer layers are separated from the central portion of the grain and discarded as bran. The proportion of the whole grain that is utilised to make flour is known as the *extraction rate*. Thus an

85 per cent. extraction-rate flour contains 85 per cent. by weight of the whole grain and 15 per cent. is discarded as bran. It is important to remember that the extraction rate refers to the proportion of the original grain in the flour and *not* in the bran. Thus flour of a ‘ high extraction rate ’ has lost little of the aleurone layer and outer endosperm.

Low-extraction flours, as compared with high-extraction flour, have the following *advantages* :

1. They are whiter. Bread made from them is more attractive to the eye.
2. They contain less fat. This makes them less likely to go rancid, so white flours are more easily preserved.
3. They contain less phytic acid. Therefore the minerals remaining in them are perhaps more readily absorbed.
4. They have better, more uniform baking qualities. Bread from them has a finer texture.

Against these, low-extraction flours have the following *disadvantages* :

1. They contain less of the B group of vitamins.
2. They contain less calcium and iron.
3. They contain less protein.

In addition, low-extraction flours contain less fibre. As the fibre is indigestible this has been claimed as an advantage. On the other hand the extra fibre in high-extraction flours adds bulk to the fæces and so has a mild laxative effect. This was known to Galen. Since Roman times much has been written about the digestibility of different types of flour. An excess of fibre may be irritating and so undesirable in certain types of gastrointestinal disorder. Some people may benefit slightly from the laxative effect. Most people will notice the effect of a sudden change from one type of flour to another ; but adaptation soon takes place. Bread made from all types of flour is smoothly and easily digested by healthy people.

Tables 17, 2 and 17, 3 illustrate the changes in the nutrient content of wheat on milling.

The advantages and disadvantages of low-extraction and high-extraction flours are beyond dispute. There is, however, a great difference of opinion between responsible and knowledgeable people as to whether the advantages of bread made from low-extraction flour outweigh the disadvantages. Moreover it is possible to overcome, at least in part, the disadvantage of low-extraction flour by the addition of minerals and synthetic vitamins ; but how effective this ‘ fortification ’ of white flour can be, is also a matter of dispute.

To appreciate these modern and sometimes acrimonious disputes it is necessary to know something of the history of milling. A digression for a brief account of this fascinating subject is required. McCance and

Widdowson (1956) have written an excellent monograph with full historical references.

TABLE 17, 2. *Effect of milling on the composition of Manitoba wheat*

Percentage extraction	Cal./100 g.	Protein	Fat	Fibre	Calcium	Total phosphorus	Phytate phosphor
		mg./100 g.	mg./100 g.	mg./100 g.	mg./100 g.	mg./100 g.	mg./100
100	328	13·6	2·5	2·2	28	350	242
85	339	13·6	1·7	0·3	19	188	96
80	341	13·2	1·4	0·1	15	139	63
70	341	12·8	1·2	Trace	13	97	30
42	341	11·8	0·9	Trace	11	82	14

From McCance, R. A., Widdowson, E. M., Moran, T., Pringle, W. J. S. & Macrae, T. F. (1945).

TABLE 17, 3. *The vitamin content of whole wheat flour and the percentage retained in flours with different extraction rates*

	Thiamine	Nicotinic acid	Ribo-flavin	Panto-thenic acid	Vitamin B_6	Biotin	Folic acid
Whole wheat flour	mg./100 g. 0·40	mg./100 g. 5·0	mg./100 g. 0·16	mg./100 g 1·5	mg./100 g. 0·40	µg./100g. 5·0	µg./100 35
Extraction rate, per cent.—		Percentage of vitamin remaining					
85	89	39	52	76	44	...	52
80	63	32	47	58	27	28	36
70	20	23	33	49	16	23	...
45	8	13	31	...	...	13	22

Data from McCance and Widdowson (1960) and Moran (1959).

HISTORY OF MILLING

"Moreover I will take from them the voice of mirth, and the voice of gladness, the voice of the bridegroom, and the voice of the bride, the sound of the millstone, and the light of the candle." Thus the prophet Jeremiah (xxv. 10) records how the noise of the millstone was a familiar sound in Biblical times. In ancient Egypt and in the classical periods of Greece and Rome, wheat was milled in large quantities between millstones of various shapes. Most of the flour produced would have been of very high-extraction rate, but loaves baked from fine white flour were certainly available in Athens and Rome. These flours were prepared by sieving (' bolting ') the coarse flours. Papyrus, rushes, horsehair and flax were used as sieves. White flour so prepared must have been very expensive, but it was appreciated by the wealthy. Both in Athens and Rome the use of white loaves in a household was a sign of prestige and position. By contrast, wholemeal bread had an appeal to some classical writers for whom it symbolised the simple life and the good countryside.

These two contradictory attitudes to white and brown bread appear to have been common for over two thousand years. In the past hundred years much evidence—reputed to be scientific—has been used to sustain both, and they have been hotly debated. It is important to realise that these attitudes are partly emotional in origin. Desire for prestige and a sentimental attachment to the idea of a simple life are powerful motives.

During the Middle Ages, in most districts of Western Europe, wheat was ground between large stones, frequently by water power. Old water-mills remain a common feature of the European countryside. Most of the flour was of high extraction, but white flour could be produced and was used by the rich. The poor followed their example whenever they could afford it. Thus Chaucer's prioress ate white bread, but the poor widow in The Nun's Tale could only afford brown. It is interesting that both of Chaucer's millers were depicted as utter rogues :—

" A theef he was for sothe of corn and mele,
And that a sly and usaunt for to stele."

The miller's reputation in mediæval England appears to have been extremely low.

In the eighteenth century, industrial developments enabled the millers to introduce many technical improvements by the use of power and machinery. Further, with the improvement in animal husbandry, they could find a ready market for their bran as cattle fodder. In consequence they were able to reduce the price of white flour. By the beginning of the nineteenth century white bread had become the accepted food of the poor.

About 1870 two important technical advances were made. The flat millstones were replaced by steel rollers between which the grains were crushed, and silk bolting cloths were introduced for sifting the flour. By these means it was possible to produce fine white flours of 70 per cent. or lower extraction rates, and consisting solely of endosperm. As Tables 17, 2 and 17, 3 have shown, there are considerable losses of certain nutrients in preparing such flours.

Highly refined white flour now became the standard material for bread-making. This pleased the millers for it gave them more bran (' offals ') to sell as cattle food ; also, since the flour was practically devoid of fat, it could not go rancid and so was easily preserved. Because of its lower nutritional properties it was less liable than wholemeal flour to infestation by beetles and the depredations of rodents. The low-extraction rates also pleased the bakers for it ensured a ' strong ' flour. ' Strength ' is a property that is apparently due to the removal of proteins rich in sulphydryl (SH) groups that are present particularly in the aleurone layer. It enables the dough to rise and so allows bread and cakes to be made with a firm, dry texture. ' Strong ' flours give the bakers the opportunity to show their art.

Around the end of the nineteenth century a variety of bleaching agents and ' improvers ' began to be added to flour. The effects of these chemicals are discussed in Chapter 24.

The great increase in the use of white flour did not take place unopposed by advocates of wholemeal flour. Graham wrote a *Treatise on Bread and Bread Making* which, published in Boston, Massachusetts, U.S.A., in 1837, was widely read both in America and Europe. He was an ardent advocate of natural foods and old-world simplicity. His ideas were sponsored by the Bread Reform League. Allinson in England, over the period 1885–1900, strongly pressed the claims of wholemeal bread in many speeches and essays. Graham and Allinson were the leaders of a considerable body of public opinion that continued to demand wholemeal bread throughout the century. Though their views were respected by everyone with a genuine interest in health, the lack of any real scientific support for their thesis, together with the wildness of some of their statements, allowed them to be too easily dismissed as cranks.

The discovery of vitamins altered this position immediately. The superiority of wholemeal over white flour could be demonstrated in a variety of experiments on animals. Moreover it was shown that in man the nutritional disorder beriberi could arise as a direct consequence of a diet in which bread made from white flour predominated. Well-attested outbreaks of beriberi from this cause occurred amongst British troops besieged at Kut in Mesopotamia in 1915 (Hehir, 1922) and in isolated Newfoundland fishing families (Aykroyd, 1930). This demonstrable deficiency of thiamine and other vitamins in low-extraction flour, and the practical knowledge of the diseases that could arise therefrom (albeit under exceptional circumstances only), convinced most nutritionists between the two world wars of the advantages of high-extraction flour. Although this view received support from an informed section of the public, in Great Britain no action was taken to control the milling of flour until 1942. The extraction rate was then increased, not for nutritional reasons, but to save space on ships taking part in the Battle of the Atlantic. When shipping space was short for carrying vital supplies of wheat from Canada and the U.S.A. to Great Britain, it was clearly absurd to use for human food only 70 per cent. of the weight of the imported grain. The Government ordered the introduction of National Flour with an extraction rate of 85 per cent. To compensate for the increased content of phytic acid, calcium was added to the flour (14 oz. of calcium carbonate to each 280 lb. of flour, *i.e.* about 0·3 g./100 g.) for reasons described in Chapter 11.

THE MODERN BRITISH LOAF

The war-time experience of Great Britain showed that it was possible to feed the country on bread made from flour of 85 per cent. extraction, which contained a large proportion of all the nutrients in the whole grain. This bread was not unpopular. It had taste which was appreciated by many, including visitors from the U.S.A. accustomed to eating bread made from 70 per cent. extraction flour. Nevertheless, the extraction rate of the flour from which the bread in Great Britain was made fell by stages and, in 1956, was reduced to the pre-war level of 70 per cent., but ' fortified ' by the addition of thiamine, nicotinic acid, iron and calcium. The decision to revert to the former extraction rate followed upon the publication of a report by a panel appointed by the Government (Panel on Composition and Nutritive Value of Flour, 1956). Prior to 1956 the extraction rate of the subsidised National Flour had been reduced to 80 per cent. The panel's terms of reference were to determine the difference in composition and nutritive value of National Flour (80 per cent. extraction) and flours of lower extraction rate with and without the addition of thiamine, nicotinic acid and iron, and to advise whether any such differences were significant from the point of view of the health of the people.

The panel concluded that " the available evidence does not reveal any ascertainable difference between National Flour (80 per cent. extraction) and flours of extraction rate less than National Flour, to which vitamin B_1, nicotinic acid and iron have been restored . . . which would significantly affect the health of the population in any foreseeable circumstance." The Government accepted this conclusion and the millers may now supply flour of any extraction rate provided the content of thiamine is 0·24 mg., of nicotinic acid 1·60 mg. and of iron 1·65 mg., per 100 g. of flour. These token nutrients can be added as pure chemicals.

The conclusion reached by the panel satisfies the demands of the millers but differs from the opinions presented by the Medical Research Council (1956). The milling industry has pressed the claim for low-extraction flour for two reasons. The first is technical. There is no doubt that it is easier to store and preserve low-extraction flour and bread made therefrom. This argument, however, does not appear to have been strongly pressed to the panel by the millers. The second reason for the millers' demand is based upon an assessment of popular opinion. The panel reported that " The (National) flour is unpopular with millers, bakers and the makers of cake and biscuits. As traders, they supply as best they can what the public wants, and as craftsmen they are anxious to maintain the traditional quality of their products. They claim to be expert judges of present public demand." The panel was thus impressed by the evidence for the demand for white flour and bread and believed that the pressure for flour whiter than 80 per cent. extraction flour was strong. They do not, however, give any evidence based on surveys of consumers' opinions to support this belief.

On the other hand the evidence that the scientific advisers to the Government and the Medical Research Council were able to give to the panel was essentially negative. A human experiment carried out on a scale never before attempted had given inconclusive results. During 1947-49 Widdowson and McCance (1954) had kept accurate records of the growth and health of groups of German children living in orphanages. They were given diets in which 75 per cent. of the calories were provided by wheat, 21 per cent. by vegetables and which contained only 8 g. of animal protein daily. The children were divided into groups receiving bread made from the following flours : (1) whole wheat, (2) 85 per cent. extraction, (3) 70 per cent. extraction, (4) 70 per cent. extraction enriched with thiamine, niacin, riboflavin and iron. The children, who were originally undernourished, grew well and flourished on these diets for a year. There was no detectable difference between the groups fed on the several types of flour. McCance and Widdowson's only firm deduction from this experiment was that wheat in any form is an excellent food for growing children. Their results show that wheat proteins are capable of maintaining high rates of growth for a long period. Bread, indeed, is a good source of protein and has been wrongly condemned as a ' starchy food.' This demonstration of the value of wheat as a source of protein for growing children is of great importance, especially for some of the countries where protein malnutrition is widespread.

These experiments do not provide much help in deciding the quality of the flour most desirable for a country such as Great Britain. Whereas in addition to the bread the German children received quantities of vegetables, a British child in a poor or broken home—eating predominantly bread—would get little or no vegetables. His diet would be made up with margarine and jam, and occasional sausages or minced meat. In periods of economic depression in the past, large numbers of children have been fed on such a diet. With economic prosperity as at present, few children are fed so badly. The Medical Research Council Conference could find no evidence that a change-over to fortified bread would result in any section of the community consuming any of the known nutrients in amounts below the allowances set out by the British Medical Association (Table 15, 1), but households with four or five children would have a very small margin of safety. It is in these households that the largest amounts of bread are eaten. The sufficiency of this safety margin when white flour is used must be in doubt.

Another cause for anxiety about white flour is that it is likely to be deficient in certain nutrients whose precise role in human nutrition is not as yet fully understood. Pyridoxine, pantothenic acid, biotin and folic acid are vitamins with important biological actions. Little is known about the quantitative human requirements of any of them. Not much is known about the amounts of these substances present in different flours, but there is no doubt that appreciable losses occur as more and more of the outer layers of the grain are removed in the milling process (Table 17, 3). For these reasons we regret the conclusion of the panel and the Government's acceptance of it, but concur with the Medical Research Council's Committee that " the consumption of a 70 per cent. extraction flour, even if this is partially fortified, would lead to a reduced intake of some nutrients. Although such a reduction would not necessarily lead to an increase in recognisable illness, it would, in the present state of knowledge, constitute a risk which can be avoided."

Future Possibilities

Lysine-enriched flour.—As Table 5, 3 (p. 83) shows, wheat gluten is poor in lysine. It is well known that young rats fed on a diet in which bread is the source of protein will grow better if given extra lysine (Hutchinson *et al.*, 1959). Lysine is now cheap and its artificial addition to flour presents no special difficulty. Lysine-enriched bread has been prepared in the U.S.A. Whether the use of such bread would confer any benefit to children or adults living on typical American or European diets is doubtful. It might well be of value for children in undernourished parts of Asia and elsewhere where wheat provides a major proportion of the calories.

High protein flours.—When the wheat grain is crushed in a mill, it breaks up into particles of varying size. The smallest particles, below 17 μ in diameter, contain a higher proportion of the protein. Apparatus has now been developed which can sift these small particles from the remainder of the flour. In this way a flour containing double the amount of protein normally present can be prepared. Obviously this is a new product which may be of considerable nutritional interest. The technology of high protein flour is already on a practical basis. Further information is given by Moran (1959).

Preparations of Wheat

Bread.—Baking is one of the most ancient of human crafts. Early in classical times there were large numbers of professional bakers in Rome, and in most cities bread-making has always been carried out by bakers ; but it is also a domestic art and before modern means of transport were available, much of the bread eaten by country folk was baked in the home. Nowadays in Great Britain there are only a few housewives—and an occasional man—who like to bake their own bread. These are usually people of taste.

Wheaten flour has the property that, after being mixed with water and made into dough, it will rise if gas is liberated in the dough either by natural yeast fermentation or from the addition of artificial baking powder. Wheat and rye alone amongst cereals can be made into bread, though other flours and even potatoes can be used to dilute wheaten flour.

However, this is not common practice, except when there is a lack of wheat.

Cultivated yeasts are generally used for the fermentation process. Young growing yeast is first mixed with sugar and a little flour. Fermentation soon begins and the yeast culture is then added to the dough and kneaded thoroughly. Fermentation is then allowed to proceed until the carbon dioxide has blown the dough up to one and a half times its original size. This may take from 1 to 4 hours, depending on the nature of the yeast culture added. The dough is then kneaded again, shaped into loaves and baked in ovens at about 450° F.

Baking powders may be used instead of yeast. These have the property of giving off carbon dioxide on moistening with water. Mixtures of sodium bicarbonate and tartaric acid are frequently used. They must be well mixed with the flour before water is added.

The protein complex gluten (a mixture of gliadin and glutelin) present only in wheat and rye, gives the dough the viscid property which keeps it together and so lets it rise when distended by gas. Good bread has a firm, strong texture and the loaf stands up well. Flours made from hard wheats such as those grown in the U.S.A. and Canada have this property of ' strength ' and make good bread. British wheat is ' weak ' and not good for bread-making though ideal for biscuits.

From the nutritive viewpoint the most important change is the dilution of the flour with water in making the dough. Most breads contain about one-third of their weight as water and their caloric value is about 250 Cal./100 g., whereas that of most flour is around 340. The protein content is also lower when expressed per unit of weight (about 8·5 g./100 g.).

Toast is made by applying dry heat to bread. This drives off some of the moisture. There are also changes in the starch grain and a little caramel is formed, which gives the colour. As water is driven off, the content of nutrients—expressed as a proportion of weight—rises. Patients on accurately prescribed diets must weigh their bread before toasting.

Biscuits are made from flours which are baked with very little water. Sometimes a small amount of baking powder is added. In the days of sailing ships, biscuits were consumed in large quantities at sea. In making modern fancy biscuits, sugar, fat, chocolate and flavouring agents may be added. Some biscuits such as Scottish shortbread contain up to 30 per cent. fat. British wheats are very well suited for biscuit manufacture. Biscuits made in Edinburgh, Reading and other towns have acquired an international reputation for quality, and large quantities are exported.

The term ' biscuit ' is employed in a different sense in the American language to mean a small, soft, unsweetened cake usually made from maize (' corn '), shortened with lard or butter and often eaten hot. In the U.S.A. British biscuits are called ' crackers.'

Crispbreads.—The original Swedish crispbreads are made with rye flour, but there are now many popular brands made with wheat. The content of water is much less than that of ordinary bread and so the caloric value is higher. Their reputation as good reducing foods is thus quite spurious. Crispbreads are a pleasant and convenient alternative to ordinary bread.

Cakes and confectionery.—These are made by baking wheaten flour with sugar and fat, to which eggs are sometimes added. Fruit and nuts may also be incorporated. Until sugar became regularly available and cheap, cakes were a luxury and, in the Middle Ages, were usually only made for feasts and festivals. Flour of high-extraction rate is not suitable for cake-making. Rich cakes may contain large amounts of fat and sugar and so are of high caloric value.

Breakfast cereals.—These are a new kind of food that has only become popular in the twentieth century. They are prepared from a number of cereals, including wheat, maize and rice. Varieties such as *shredded wheat* and *grapenuts* are made from whole wheat. Breakfast cereals are not usually eaten in large amounts, but people appreciate their palatability, their ready cooked state and the attractive packages. Their chief nutritive value is that they are always eaten with milk. There are many children who do not like milk as a drink, but will consume a large amount with their daily breakfast cereal.

Semolina is prepared by crushing wheat and extracting the broken endosperm. It has the nutritive value of a very low-extraction flour and is much used for making puddings.

Macaroni, spaghetti and vermicelli.—These and other forms of Italian ' pasta ' are made from a very hard variety of wheat (*Triticum durum*) which flourishes in the hot, dry Italian climate. Only the endosperm is used for making flour for ' pasta,' which is not rich in the B group of vitamins. Their very high gluten content enables the characteristic mouldings to be made.

Thus far we have described European methods of preparing wheat. In Asia and North Africa wheat is often eaten as unleavened bread. The flour used is usually of high extraction, often milled in the home.

Chappatis are the common form in which wheat is eaten in India, Pakistan and Iran. They are made from wholemeal flour (atta). Coarse sieves remove some of the fibre and bran. This may amount to 5 to 7 per cent. of the total weight. So Indians usually eat 93 to 95 per cent. extraction flour (Patwardhan, 1952). One method of making a chappati is as follows : The dough is first prepared by mixing the atta with water and kneading. Usually salt and a little oil are added. A portion of the dough is rolled on a wooden board until it is flat, thin and circular. It is then placed on a flat iron pan over an open fire and slowly cooked. When one side is done, the chappati is turned over and the other side cooked. There are many minor variations in technique and chappati-making is a subtle art. Those made by an expert are soft and tasty with the delicious flavour of whole wheat.

Puris are made from chappatis by rolling a small flat piece and then frying it in deep butter-fat. As butter-fat is expensive, puris are regular food for the rich only. On festive occasions they are made by all classes and are very much appreciated.

RICE

Pictures of rice cultivation are shown in Plates VIII and IX. The rice grain has approximately the same botanical structure as the wheat grain. Hinton (1948 *a*) has made beautiful micro-dissections (Plate VII) and gives the following analysis for the thiamine content of the components of the individual grains (Table 17, 4). It will be seen that the pericarp, aleurone and the scutellum together contain 79 per cent. of the total thiamine present in the grain, although constituting only 6·2 per cent. of the weight. By contrast the endosperm, which represents 92 per cent. of the grain by weight, contains only 8·8 per cent. of the thiamine.

TABLE 17, 4. *Thiamine content of fractions of the rice grain*

Part of grain	Proportion of grain	Thiamine content	Proportion of the total thiamine of the grain
	Per cent.	μg./g.	Per cent.
Pericarp and aleurone	5·95	31	35·2
Covering to germ	0·20	12	
Epiblast	0·27	78	3·9
Coleorhiza	0·20	94	3·5
Plumule	0·31	46	2·7
Radicle	0·17	62	2·0
Scutellum	1·25	189	43·9
Outer endosperm	18·80	1·3	8·8
Inner endosperm	73·10	0·3	

Changes similar to those already described for wheat occur when rice is milled. These changes are of immense public health importance because rice so often forms such a large proportion of the total food of rice-eaters. Full accounts of the chemical properties of rice in relation to the nutritive value of rice diets are given in two monographs (Aykroyd *et al.*, 1940; FAO, 1954 *a*).

From time immemorial a variety of methods have been used by men for husking 'paddy'—the rice grain in the husk. The domestic labour of preparing rice by hand-pounding is still undertaken in most parts of the East. The paddy is placed in a stone or wooden mortar, about 6 in. in diameter and 8 in. deep, and pounded with wooden pestles about 6 ft. long. Usually two or more people pound together. The pounding breaks the outer husk and allows it to be separated by winnowing. Some of the germ and part of the pericarp is removed, the amount depending on the vigour and duration of the pounding. It is possible to produce a refined white rice almost totally devoid of vitamins by home-pounding. Yet rice so pounded normally retains over half of the outer layers of the grain, thus conserving the greater part of the vitamins. Home-pounded rice is essentially a high-extraction cereal grain and a satisfactory source of B vitamins. However, pounding is a wearisome domestic drudgery even if, as in many parts of Bengal and Thailand, a simple mechanical device enabling the mortar to be worked by the feet is used. It is therefore not surprising that mechanical rice mills have sprung up and are slowly but steadily spreading among the rice-eating people. The housewife is relieved of domestic labour, at no financial cost since many mills are content to retain as their fee the bran removed, which is sold as cattle fodder. Mills can produce a highly refined rice, almost devoid of vitamins as Table 17, 5 shows.

TABLE 17, 5. *Thiamine content of rice at different stages of milling*

	μg./g. of rice
Husked only	4·0
Once polished	1·8
Twice polished	1·0
Thrice polished (ready for market)	0·7

Parboiling.—There is, however, one process which is widely applied both in the home and in the mill in the preparation of rice, which has a profound effect upon the content of the B group of vitamins in the final process. This is known as ' parboiling,' which means the steaming or boiling of unhusked rice after preliminary soaking. This process splits the woody outer husk and renders its subsequent removal easier. Small quantities of paddy may be parboiled in domestic vessels before pounding. In the bigger mills it is steamed under pressure in large cylinders. The parboiling either drives the vitamin into the interior of the grain or may fix the scutellum so that it is less readily removed in the milling process (Hinton, 1948 *b*). In any case the result is to fix the vitamins so that they are not removed with the bran and remain behind in the milled grain. This result is shown graphically in Fig. 17, 2, which depicts the effect of varying degrees of milling upon the two samples of the same paddy, one parboiled and one raw. It will be seen that even in very highly milled samples of parboiled rice the major portion of the thiamine is still present. Similar results are obtained for nicotinic acid. This is of profound importance for, as Chapter 32 explains, in all parts of the world where rice forms the major staple article of diet, beriberi is constantly liable to break out, except in those countries or states where it is the usual custom of the people to parboil the rice. The parboiling of rice is the simplest and most effective preventive measure against beriberi. There is no doubt that the disease could be eradicated almost completely and an improvement in general health achieved, if an effective control could be put on rice mills by insisting on *either* the parboiling of all paddy *or* a limitation on the degree of milling. The statutory control of wheat mills in Great Britain has presented many difficulties; similar government controls in the tropics would present even greater administrative problems. Chief of these is the lack of suitable supervisory staffs and analytical laboratories for checking the products of the mills. In most tropical countries, as in Great Britain, there is insufficient educated public opinion to support any government in instituting measures which must be unpopular with the powerful milling interests. As in the case of wheat, objections have been raised to the under-milled rice on the score of its indigestibility. Again, complaints rest on the slenderest basis of fact, namely the slight laxative effect of the bran. Rice accused of producing indigestion is often the same as that consumed by millions of people elsewhere without complaint. The truth is that all ordinary rices and rice preparations can be digested satisfactorily by healthy people. The human digestion (or more probably the human mind) is essentially conservative and any change in the diet is temporarily resented.

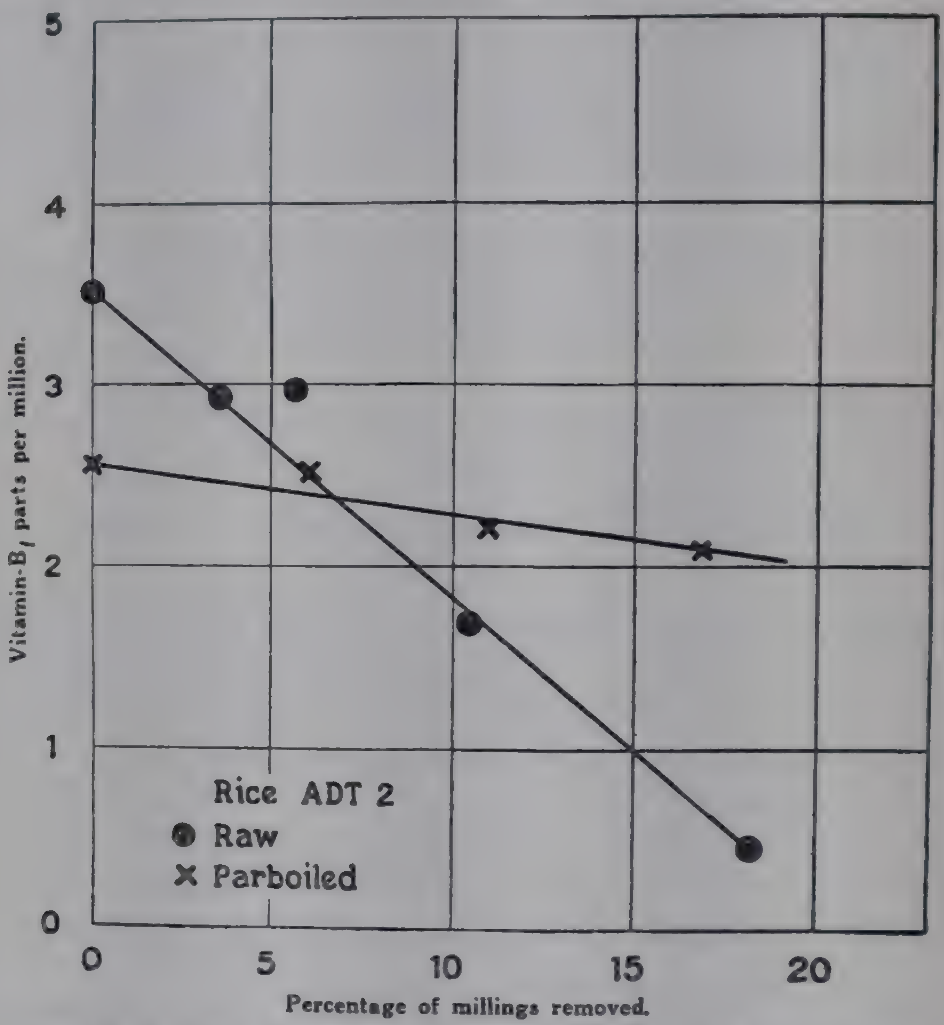


FIG. 17, 2. The effect of milling in the raw and parboiled states on thiamine content of rice. (AYKROYD *et al.*, 1940).

In addition to milling, the rice grain is subject to another severe loss of vitamins in the washing and cooking of the cereal. Rice, purchased in the bazaar, must be washed in the home before cooking, which itself involves the use of water. Much of the water is often subsequently discarded. The B group of vitamins are all very soluble in water and heavy losses may thus result in the home. Experiments conducted under cooking conditions common in South India showed that half the thiamine and nicotinic acid that escaped the mills might be thrown away as domestic waste. Even higher losses may occur. Such losses can be reduced, first by seeing that rice reaches the home as clean as possible; this requires clean and good storage conditions in the shops and bazaars. Secondly, within the home a minimum of water should be used for cooking, and all surplus should not be discarded but taken as the drink known as 'congies.'

The enrichment of rice

A pioneer venture in the 'enrichment' of rice was carried out in the Philippines soon after the 1939–45 war by Salcedo and his colleagues (1948). The great ease with which substances can be removed from rice by washing constitutes a technical difficulty in adding nutrients to rice. It was hoped that this might be overcome by the technical device of adding manufactured 'Premix' grains. These grains were said to contain thiamine 0·85 g./kg., nicotinic acid 7·04 g./kg. and iron 5·72 g./kg. They could be mixed with the rice from commercial mills and in the proportion of 1 in 200 were thought to be sufficient to ensure an adequate intake of these nutrients with the rice. If riboflavin were added, the Premix grains were conspicuous by their yellow colour and could easily be picked out and discarded by the ignorant or prejudiced consumer.

In this field trial, carried out on the Bataan Peninsula, two population groups were studied. During the year before the trial the first group had 167 deaths from beriberi with a death-rate of 263 per 100,000, and the second group 43 deaths with a death-rate of 149. During the experimental year the first group received 'enriched' rice, and deaths from beriberi fell to 74 with a death-rate of 117. In the second group, which acted as a control, the deaths numbered 48 and the death-rate rose slightly from 149 to 163.

There can be little doubt that under the conditions existing in the Philippines at the time of the trial, the fortified rice was of value in reducing mortality. However, the great majority of the deaths from beriberi were infants. The figures cannot be very reliable as the diagnosis of infantile beriberi as a cause of death is seldom easy.

An international team visited the Philippines and reported (FAO, 1954*b*) on the experiment. The team was very cautious in recommending 'enrichment' to other Asiatic countries and pointed out the following obstacles :—

1. The dependence of most countries on overseas sources for the supply of the necessary synthetic vitamins and perhaps minerals renders the process extremely vulnerable. Although the cost on an individual basis is small, its cost on a national basis is large.

2. Ensuring that the Premix is added to the milled rice in the correct proportions in the different types of rice mills is difficult. Unless this can be suitably controlled, there is no guarantee that the added nutrients will reach the consumer in the quantities desired and the whole process of enrichment will be frustrated.

3. Undoubtedly the difficulties in the mills arise partly out of the somewhat unsatisfactory construction of the Premix feeders, partly from the inexperience, negligence, carelessness and possibly, at times, dishonesty of the millers. To overcome them an elaborate system of control and inspection of all mills would be essential.

Other Asiatic countries appear to have been in no hurry to undertake an ' enrichment ' programme. India in particular has not been impressed by the Philippines experiment. Further trials have been carried out with American assistance in Taiwan (Formosa), but the report (Huang & Tung, 1955) of the results is anything but convincing as scientific evidence of its value.

A beneficial effect of rice ' enriched ' with thiamine, nicotinic acid and riboflavin has been shown in a trial (Crowley *et al.*, 1956) on Chinese troops in Taiwan. Five hundred men received ' enriched ' rice for a period of six months and a control group of a similar number were on the same ration-scale but received ordinary milled rice. There was a marked fall in the incidence of glossitis, naso-labial seborrhœa, scrotal dermatitis and angular stomatitis in the men receiving the enriched rice, but the incidence of these conditions in the control group remained at the same high level as at the start of the experimental period. Thus ' enrichment ' of the rice brought about a marked remission of the signs attributed to riboflavin deficiency. The Premix grains contained riboflavin (which makes their colour unacceptable to some people) and so brought the riboflavin content of the rations up from the control value of about 0·9 mg./day to about 4·6 mg./day.

An enthusiastic account of the possibilities of eliminating beriberi by a policy of rice enrichment has been given recently by Williams (1961). The serious student of this subject should read his monograph and compare it carefully with the cautious FAO report.

We are satisfied that rice ' enrichment ' with Premix can, under certain circumstances, be a practical and useful temporary measure. A serious outbreak of beriberi in a region might well be a legitimate reason ; but we would agree with the FAO team about the practical difficulties of an ' enrichment ' policy on a national scale.

Apart from the practical difficulties, the same general objections hold for a policy of ' enriching ' rice as for the ' enrichment ' of wheat. It is only possible to replace by chemicals a portion of the nutrients that the millers remove. Genuine concern for the physiological value of the discarded portion must be far greater in the case of rice, because the diets of rice-eaters are so often poorly balanced in other respects.

MAIZE

An excellent account of maize and maize diets has been prepared by FAO (1953*a*) with the assistance of Dame Harriet Chick. What follows is for the most part an abstract of this.

Maize cultivation originated in the New World, but was soon brought across the Atlantic by explorers early in the sixteenth century. A hundred years later it was well established in countries both on the north and south shores of the Mediterranean Sea. Later, maize cultivation spread very widely in Africa and in many parts of Asia ; at about the same time its production in the Southern States of the U.S.A. greatly expanded.

Maize is in general much more resistant to drought than either wheat or rice. In addition it gives a high yield per acre. It matures rapidly so that a good crop can be grown in a short season. For these reasons maize has acquired a well-deserved reputation as a poor man's cereal. In countries with a well-developed agriculture, it is mostly used as a food for cattle and poultry.

The maize grain has the same general structure as that of rice and wheat. The following preparations are used as human food.

' Corn on the cob ' is the cooked, freshly picked grain and a popular adjunct to a meat meal throughout the U.S.A.

Whole maize grain.—This is the whole grain which is removed from the cob after drying, usually in the sun.

Whole maize meal.—Whole maize grain is ground to meal fineness either by hand-pounding or by modern techniques. The meal is not subjected to any ' bolting ' and contains 97 to 100 per cent. of the original grain.

Decorticated maize meal.—This is the wholemeal with most of the pericarp, but none of the germ, removed by sieving or simple fanning. It usually contains 90 to 96 per cent. of the original grain.

Degerminated maize meal.—The wholemeal is passed through finer sieves, which remove most of the pericarp and germ. It usually contains about 85 per cent. of the original grain.

Hominy or samp.—This is the starchy portion of the endosperm, left after the whole grain is softened by steaming, the pericarp removed and the germ loosened by a handling machine. In the U.S.A. hominy grits are produced by dry milling. In South Africa samp signifies the endosperm. Samp and hominy thus resemble refined products of rice and wheat. However, they do not appear to have acquired the same social prestige as the latter. The processes for maize milling are almost as varied as those for rice and wheat and are associated with similar losses in the B group of vitamins.

Hominy chopis is the name given to a product consisting mostly of bran.

Maize may be boiled and made into a porridge. This is the usual method in Europe and Africa. *Polenta* is an Italian maize porridge to which cheese or lard is added. *Zgance* and *projaca* are names for Yugoslav maize dishes, in which eggs and cheese may be mixed with maize. '*Stamp and go*' is a Jamaican dish in which maize porridge is mixed with a little meat or fish, and pepper or other condiments. Maize may also be made into flat bread. In preparing Mexican *tortillas*, the grains are softened by heating in lime-water and then ground directly into a dough and cooked on a hot iron plate. The lime may provide an important contribution to the calcium intake of the consumer.

Maize itself will not make leavened bread, but it can be mixed with wheat flour and baked into good loaves. This is common practice in the Middle East and Southern Europe. It has been widely adopted in all parts of Europe when wheat is scarce.

The nutrient value of maize resembles that of other cereals in general, but differs in some important respects. Unlike other cereals yellow maize contains carotenes which are precursors of vitamin A and different varieties have been found to have vitamin A potencies ranging from 300 to 400 i.u./100 g. These are significant amounts. Evidence of severe vitamin A deficiency is rare in poor populations dependent on yellow maize as the chief item in their diet. The principal protein in maize is zein, which forms about half the total protein in the whole grain. Zein is an imperfect protein, lacking lysine and containing very little tryptophan. This defect is important in the relation of maize to pellagra (Chapter 34). Truswell and Brock (1961) record the effect of supplementing the protein of whole maize on eight normal men accustomed to eating large quantities of maize. The basic diet provided about 0·9 g. protein per kg. of body weight. On maize only the subjects were in approximate nitrogen equilibrium. Adding simultaneously to the diet lysine, tryptophan and isoleucine, caused a mean daily increase of just under 0·5 g. in nitrogen retention. Many varieties of maize contain less tryptophan than the sample used in this trial. A supplement for maize protein should contain both lysine and tryptophan and (if possible) isoleucine. Fortification of maize with these amino acids might be a practical measure in some countries. Most varieties of maize contain less nicotinic acid in the whole grain than other cereals, but rice diets may contain no more than maize diets, owing to the loss in cooking and washing.

MILLETS

Plate XI shows millet cultivation in North Africa and Plate X a millet granary. The millets are cereals which are very resistant to drought and so have been extensively cultivated in arid regions. They are the staple food of many people in Africa and also in some areas of Asia and Latin America. With the spread of irrigation and the introduction of drought-resistant varieties of wheat, millet cultivation is tending to decline, notably in India. Millets have always been regarded as a poor man's food and there are social prejudices against their use. Although this is understandable (they are much less tasty than wheat or rice) it is unfortunate, for they have good nutritive value and their protein is a valuable addition to rice protein in predominantly rice diets.

There are a variety of different millets which have an even greater variety of names. Common millets are (1) *Sorghum vulgare*, often known as the large millet, or sorghum. In India, where it is widely grown, it is known as *juar* in the north and *cholam* in the south. (2) *Eleusine coracana* is known as *finger millet* in Africa and as *ragi* in South India. (3) *Pennisetum typhoideum* is widely grown in India and known as *bajra* in the north and *cambu* in the south. There are a variety of names for it in use in Africa ; it is often referred to in scientific literature simply as ' millet.' These are the three most important millets in Africa and Asia. In South America *quinoa* (*Chenopodium quinoa*) is a hardy millet which is widely grown in the cold arid countryside on the altiplano. Many other species of millets are grown locally but extensively in many districts of the world.

Millets, like all other cereals, have to be husked. The grains may then be soaked and boiled and made into a porridge or ground into a meal. These processes are usually carried out in the home since millet-eaters are mostly simple peasants. Refined millet products have not yet appeared on any international market on an appreciable scale.

OATS

In Scotland oats became the staple food of the people in the seventeenth and eighteenth centuries, gradually replacing barley and rye. In the nineteenth century oats were in turn gradually replaced by wheat. Oatcakes and brose (uncooked oatmeal treated with water, milk or whisky) ceased to be common daily foods, while porridge survived chiefly as a breakfast dish. In the twentieth century oats have been largely ousted even from this limited position by the ubiquitous breakfast cereal ; in 1947 we found that only 20 per cent. of male and 8 per cent. of female Edinburgh undergraduates, living at home, ate porridge for breakfast. Even in the Highlands there are probably few families left who still take their porridge daily, one reason being the virtual extinction of local milling consequent on the decline of the population.

In the milling of oats only the fibrous pericarp is usually removed and the germ is retained. Most forms of oatmeal are thus not highly refined. Frequently nowadays the grains are not ground, but crushed flat between rollers. Heat is applied during the process and the grains are thus partially cooked. The resulting ' rolled oats ' are the basis of several convenient breakfast preparations.

Oats have much the same general composition as wheat. A considerable proportion of the phosphorus is in the form of phytic acid. This is said to interfere with the absorption of calcium, but as discussed on page 161 it is doubtful if this is important in human nutrition. Children brought up in Highland crofts on large quantities of porridge were not rachitic.

Only when the crofter migrated to Glasgow, where he usually changed from oatmeal to white bread, did his family develop rickets.

In Scotland at least, a variety of special virtues have been attributed to oatmeal. It was believed to be good for diabetics and people with sluggish intestinal movements. As far as we know there is no scientific justification for these beliefs. On the other hand, oatmeal is a good wholesome food ; it contains slightly more protein, calcium and fat than any other cereal (Table 17, 1).

The decline in the consumption of oatmeal is probably attributable in the main to a change in cooking habits. Proper porridge needs to be prepared the night before and left to warm on the hob of the kitchen fire overnight, or in the haybox. The introduction of gas and electric cookers has abolished this traditional practice, and although proprietary brands of rolled oats can be made into porridge in a few minutes before breakfast, a ready-cooked breakfast cereal or a loaf of wheaten bread is less trouble for the modern housewife working with one eye on the clock.

BARLEY

Barley is widely grown in almost all parts of the world. It was once much used as a human food. It produces the most satisfactory malt for brewers and is the basis of the best beers and much whisky in many countries. It is widely used as a cattle food.

RYE

Rye was once a common crop all over Europe and is still widely grown in the north-east. It is resistant to cold. It has long ago ceased to be a staple crop in Western Europe. When Robert Burns adapted the old song 'Coming through the Rye' it was already something of an anachronism. His own song ' Corn Rigs an' Barley Rigs ' sounded the true contemporary note. Rye bread is coarser, harder and darker than wheaten bread.

[Unfortunately the above paragraph from the first edition contains an error. The rye to which the poet referred was not the cereal but a small stream in his native Ayrshire. In this stream young girls might get their petticoats wet when going to meet their boys.]

CHAPTER 18

STARCHES AND STARCHY ROOTS—SUGARS AND SYRUPS—PULSES, NUTS AND SEEDS—VEGETABLES—FRUITS

IN the following chapters of Part II we give some account of the origin of the other principal foods of man—where they are grown and how they are processed. We also give some assessment of their qualities, not only in terms of their chemical constituents but also in those special properties that go to make good food as the connoisseurs know it. Here we have drawn heavily on the account given by Mottram and Graham (1956) and would advise readers who wish to learn more about the nature of foods to consult their excellent chapters on this subject.

1. STARCHES AND STARCHY ROOTS

The potato is the most important food of this class in temperate climates. In the tropics cassava (also known as manioca, yuca and tapioca), the yams, the sweet potato and taro are all important foods. (Sago, as it is very rich in starch, is usually classified with these foods, though in fact it is derived from the pith of a palm.) Arrowroot and a large number of other roots are also eaten in small quantities in the tropics. Such roots all contain large quantities of starch and so are good sources of energy. For the most part they are poor in protein, minerals and vitamins. They are easily cultivated, often giving high yields even on poor soil, and so have been widely used by peasants in many parts of the world. The common garden root vegetables contain much less starch and are discussed on page 295 under Vegetables. Plate XII, A, shows a typical cassava plantation in the tropics and Plate XII, B, a market.

Table 18, 1 gives values for the principal nutrients in starchy roots. In this and subsequent tables for other classes of foodstuff, a range is given for each nutrient. The most important foods in the class fall within this range. The tables are intended to show what contribution the foods concerned can make to daily intakes of each nutrient. A few important individual foods falling outside this range are separately listed. A selected value is also given for each nutrient. This may be used for calculating the nutrient content of diets in which the individual foods are not specified in detail. Ration scales for institutions and armed forces for instance, usually lay down the allowed quantity of each class of foodstuff, but often do not specify the individual foods.

TABLE 18, 1. *Starchy roots*

Potato, sweet potato, yams, taro

(Composition in terms of the retail weight, as purchased.)

	Range	Selected value	Notes
Moisture, per cent.	65–85	...	...
Cal./100 g.	50–125	80·0	...
Carbohydrate, g./100 g.	10–25	18.0	...
Protein, g./100 g.	1·5–2·5	2·0	Tapioca and sago as sold in Europe, 0·3–0·4
Fat, g./100 g.	Trace	0	...
Calcium, mg./100 g.	10–30	20·0	...
Iron, mg./100 g.	0·5–2·0	0·8	...
Vitamin A, i.u./100 g.	0	0	Sweet potato: most varieties 500; deep yellow and red up to 7000
Ascorbic acid, mg./100 g.	5–25	15·0	...
Thiamine, mg./100 g.	0·05–0·10	0·075	...
Riboflavin, mg./100 g.	0·03–0·08	0·05	...
Nicotinic acid, mg./100 g.	0·5–1·5	1·0	...

The common potato (*Solanum tuberosum*)

This is a native of the New World. It flourished and continues to flourish on the *altiplano* in the Andes and was the staple food of the peasants under the Inca civilisation. It was introduced into Europe by the early explorers—at first as a curiosity. However, it spread rapidly throughout the European continent in the second half of the seventeenth century and in the eighteenth century. The introduction of the potato was initially a great blessing since it provided the peasants with a cheap alternative crop to cereals. Until the eighteenth century the history of all European countries was marked by famines due to failure of the main cereal crops as a result of drought or disease. Potato cultivation provided a second crop which allowed a population to survive despite a failure of the cereal harvests. The last serious famines in Scotland were during the 'six dear years' of William III's reign at the end of the seventeenth century, prior to the extensive cultivation of potatoes. In Ireland the potato flourished exceedingly well and completely ousted cereal crops. The peasants became entirely dependent on one food crop again, and they paid the inevitable penalty. The potatoes were attacked by the blight (*Phytophthera infestans*); the harvest failed for three years from 1845 to 1847 and the people suffered one of the most disastrous famines in history. The population fell from 8·2 million in 1841 to 6·6 million in 1851. Probably over one million died and many were forced to emigrate. Ireland has not yet recovered her former population and Boston, Glasgow and many other cities owe a large part of their present population to the direct effect of the potato blight.

The potato has two remarkable properties. First, it is the only single cheap food that can support life when fed as the *sole* article of diet. Hindhede (1913) describes a man who lived on a diet of 2 to 4 kg. of potatoes daily with a little margarine as the only other source of food for 300 days. Secondly, potatoes yield more calories per acre than any cereal crop. The importance of this fact to an eighteenth-century peasant can be illustrated by some calculations from data collected by Young (1771) of average yields on English farms.

TABLE 18, 2. *Average yields from English farms in the eighteenth century*

	Average annual yield per acre		Caloric value of crop	Acres required to provide 10,000 Cal. daily for a year
	Bushels *	kg.	million Cal.	
Wheat . . .	23	650	2·1	1·7
Barley . . .	32	820	2·7	1·4
Oats	38	690	2·2	1·6
Potatoes . . .	427	10,900	7·6	0·5

* Young's figures for 1771. With modern agricultural techniques all yields per acre are higher, but the difference between potatoes and cereals still holds.

The first column gives Young's data in bushels, a measure of volume. The second column gives the weight of the crops and the third their approximate caloric value. The last column gives the amount of land required to provide the total caloric needs of a family of a man and wife with three young children (estimated at 10,000 Cal./day). Thus the peasant needs less than half as much land to feed his family if he grows potatoes in place of cereals as his main crop. He also needs less land for his subsidiary crops to provide protective foods. These conditions are ideal for the landlord. Salaman (1948) in his classic book on the history of the potato has pointed out that in ' potato civilisations ' the peasants have been at the mercy of their landlords. Probably at no time in history has man been reduced to more misery and abject poverty than the South American peasants under their Inca rulers and the Irish under their English landlords.

In modern Western civilisations the potato has established its position as a cheap and popular food appreciated by both rich and poor. Potatoes contain 75 to 80 per cent. of water and yield from 70 to 90 Cal./100 g. Of the calories, 7·6 per cent. comes from protein, a negligible amount from fat and most from starch. The protein content is low but the total amount of protein provided by potatoes is by no means negligible, especially if large amounts are eaten.

The figures usually given for the protein content of potatoes are not strictly correct. They are obtained by multiplying the total nitrogen content by the conventional figure of 6·25. In fact less than half the nitrogen in potatoes is present as protein (Neuberger & Sanger, 1942). There are fairly large amounts of asparagine, glutamine and arginine. The nutritional significance, if any, of this distribution of nitrogen is unknown.

Potatoes contain small but not very important amounts of minerals and the B group of vitamins. They are a good source of potassium. Potatoes are not rich in ascorbic acid, but when they are eaten in large quantities they often provide a considerable proportion of the ascorbic acid in the diet. However, their ascorbic acid content is very variable; figures ranging from 4 to 50 mg./100 g. are given in the literature. This wide variation is due, in part at least, to losses in storage. A figure of 30 mg. or over will only be found in freshly dug potatoes, whereas from March until the new harvest values will usually be below 10 mg. This seasonal variation can be important. In Edinburgh for instance, where patients with scurvy are occasionally seen, they appear usually in the spring and early summer. They are almost always old men living alone. The disease is seldom found after the new potatoes arrive in the shops; they probably serve to prevent scurvy throughout the autumn and winter.

The effect of cooking on the ascorbic acid content of potatoes is discussed in Chapter 22.

Potatoes are easily digested and well absorbed and are thus a good food for invalids. They are a valuable and useful food with an important place in the British diet. Their reputation for being fattening is perhaps undeserved. They do, of course, form fat if eaten in amounts sufficient to make the caloric value of the diet greater than the daily energy expenditure. But so do all other foods.

Cassava (*Manihot utilissima*)

These shrubs, of which there are several species, are natives of South America, but are now widely grown in Africa and some parts of Asia. Cultivation is easy, new trees being propagated from stem cuttings. When they have grown to a height of 10 to 15 feet they are dug up and the tubers or thickened roots cooked. The roots when damaged may become poisonous owing to the presence of cyanides, which have to be removed by washing and drying in the sun.

Cassava is the principal food of many people in the tropics. The fresh root contains 50 to 75 per cent. of water, less than 1 per cent. of protein and the remainder mostly starch. Only about 3 per cent. of the calories are derived from protein: this is less than half of the proportion of calories derived from protein in potatoes, yams and taro. This low-protein content places cassava in a different nutritional class from the other starchy roots. Protein malnutrition is common in all communities dependent on cassava. As an easily cultivated food providing energy it is a valuable crop for many people; but it should only be cultivated along with other crops which can provide additional protein.

Tapioca as sold in Western countries is a preparation of cassava rom which most of the protein is removed: in fact it is almost pure tarch.

Yams

The two most important cultivated varieties are the greater yam (*Dioscorea alata*) and the lesser yam (*Dioscorea esculentia*). Both are climbing plants. The tubers take four to twelve months to develop. Those of the larger species are big and may be as large as a football. The lesser yam has clusters of smaller tubers. Several wild yams may also serve as a source of food.

Like potatoes, the yam tubers are rich in starch, but also contain significant amounts of protein.

Sweet potato (*Ipomœa batatas*)

This herbaceous plant with starchy tubers is extensively cultivated in the southern states of the U.S.A. and other hot climates. The crop is propagated from stem cuttings and the tubers weigh up to 1 lb. each. They have the same general properties as the potato and when fresh may contain up to 30 mg./100 g. of ascorbic acid. Many varieties are coloured either red, yellow or purplish-yellow. The pigment is carotene and in some communities the sweet potato may be an important source of vitamin A activity in the diet.

Taro (*Colocasia esculentia*)

This is widely grown in the Pacific Islands and in parts of Africa and Asia. It is also known by various local names such as *dasheen*, *eddo*, *keladi* and *cocoyam*. The *Colocasia* plant is a herbaceous perennial with tubers 6 to 12 in. long, which are used for propagation. They have the same general nutritive properties as yams and potatoes. The young leaves and stalks are also eaten as fresh vegetables.

Sago

This is obtained from the pith of the sago palm (*Metroxylon sagu*) which is widely grown in Malaya, Indonesia and other parts of the Far East. The tree has to be felled and split before the starch is washed out. The commercial preparations (' pearl sago ') are almost devoid of protein.

Invalid foods

Sago, tapioca, arrowroot and ground rice have each some reputation as 'invalid foods.' The commercial preparations on sale in temperate countries are almost pure starch. Provided it is realised that these foods are almost devoid of proteins, minerals and vitamins, they are useful as easily assimilated sources of energy. Taken with a suitable source of protein, as in milk puddings, they are valuable foods for the sick and also for young growing children.

2. SUGARS AND SYRUPS

During the last hundred years the consumption of sugar in Great Britain has risen sixfold and is now about 120 lb./head/year. Until the eighteenth century sugar was a luxury acquired from the sugar-cane grown in tropical or semitropical areas in the East. During the Middle Ages cane sugar was part of the spice trade that came from the East to Venice and so into Europe. In the thirteenth and fourteenth centuries the price of sugar lay between one to two shillings a pound—more than a week's wages for a servant. It was much in demand by apothecaries for making their confections. The supply increased with the development of the sugar colonies—the West Indies and the Atlantic Islands. In the middle of the seventeenth century the presence of cane sugar in beetroot was discovered by the German chemist Margraf, and during the Napoleonic Wars much sugar beet was planted in France with a view to achieving independence from outside sources. During the nineteenth century sugar beet cultivation was greatly extended in Germany and France and more recently in Great Britain. There was also a great increase in imports of sugar from cane grown in the colonies.

Sugar is readily preserved and so is very suitable as an article of trade. This, together with its cheapness and its usefulness as a flavouring agent, made it most popular with the new industrial urban populations. As a cheap and easily digested form of energy, sugar is a valuable food ; but as it lacks every nutrient save carbohydrate, its very attractiveness is a danger in that it tends to displace other more nutritious foods from the diet. Coincident with the increase in the sugar consumption there was an increase in the incidence of dental disease. This is further discussed in Chapter 54.

Chemists have devoted much technical ingenuity to removing the last traces of ' impurities ' from commercial sucrose, even employing animal charcoal as a clearing agent to precipitate the minute amounts of coloured matter that are naturally associated with it. Crystalline table sugar is thus one of the purest chemicals regularly produced in large quantities by modern industry. It is practically 100 per cent. sucrose and contains no other nutrients, such as minerals or vitamins. ' Brown sugar ' is less highly refined sucrose containing traces of other sugars and colouring matter ; perhaps for this reason it has a better natural flavour and is especially esteemed for use in coffee. Public demand for brown sugar has sometimes tempted the manufacturers to produce a spurious imitation of it by simply adding a synthetic brown dye. The raw sugar cane that is chewed in considerable quantities—especially by children—in the sugar-growing areas of the tropics contains only traces of protein, vitamins and minerals.

Syrups are highly concentrated solutions in which the sugar is unable to crystallise out owing to the presence of small quantities of other substances. They include molasses, treacles and golden syrup which are

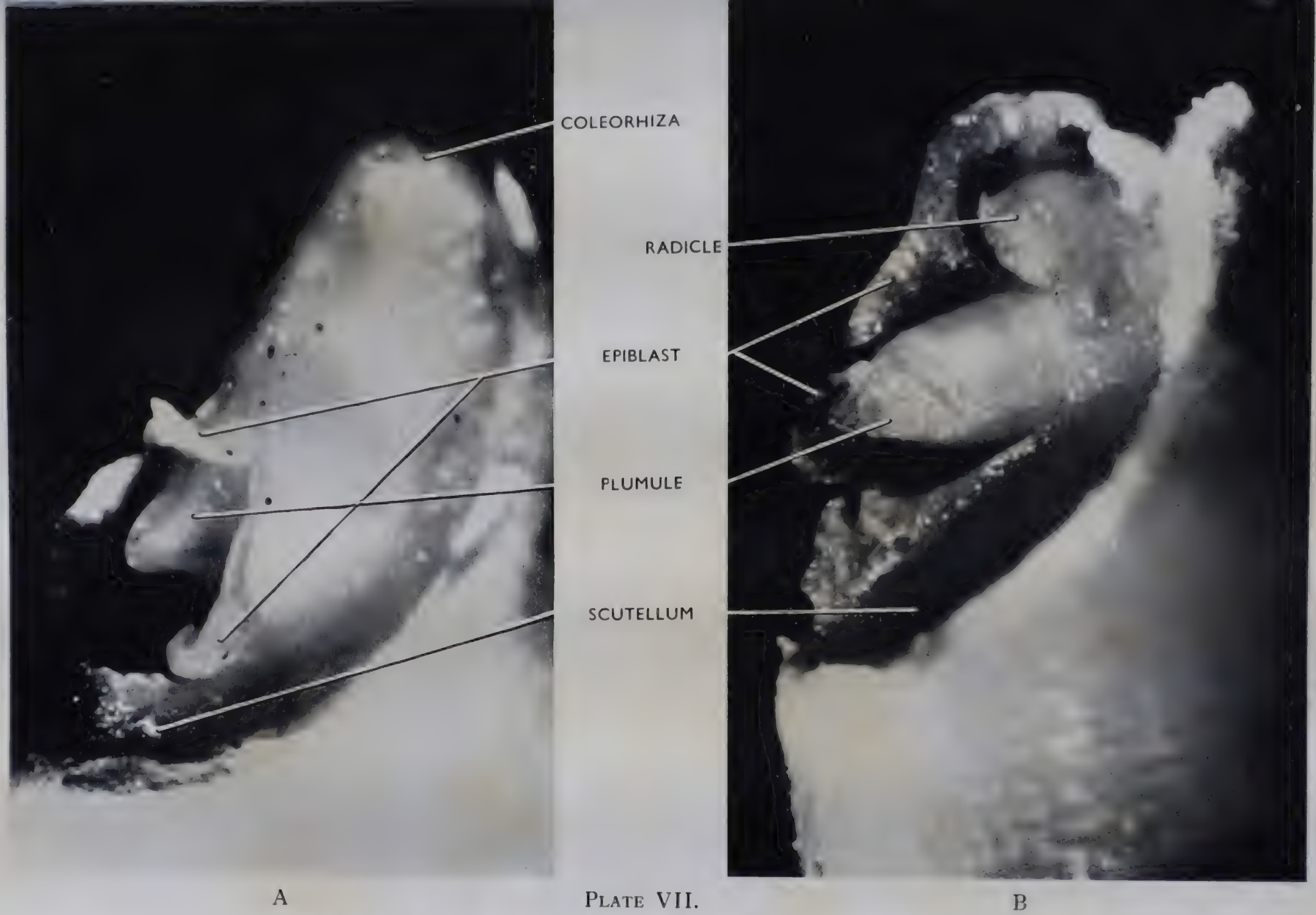


PLATE VII.

A, Surface view of the embryo of the rice grain. B, Dissection of the embryo of the rice grain. From the *British Journal of Nutrition* (HINTON, 1948 *a*).

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PLATE VIII. Rice terraces in Java. (From FAO photo by S. Bunnag.)

Plate IX. Transplanting rice in Thailand. (From FAO photo by Eric Swab.)

Plate X. Sorghum and millet granary in the French Sudan.
(From FAO photo by M. Ganzin.)

PLATE XI. Improved strains of the millet *Penniseturm typhoideum* growing in Libya. (From FAO photo.)

PLATE XII A. Plantation of yuca (cassava or manioca).
(From FAO photo by L. E. Campbell.)

PLATE XII B. Cassava market in French Togoland.
(From FAO photo by M. Ganzin.

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by-products of the manufacture of crystalline cane sugar. These contain 20 to 30 per cent. of water in addition to sugar. They may also contain nutritionally significant amounts of calcium and iron, some of which probably comes from the vessels in which they have been processed.

Various natural syrups exist of which perhaps the most famous is the maple syrup obtained from the sap of the maple in Canada and New England. It contains about 20 per cent. of water and the remainder carbohydrate.

Honey is a pleasant attractive food. At many times and places it has acquired a special reputation either as a medicine or as a nutritious food. Unfortunately this reputation is undeserved. Most honeys consist of about 20 per cent. water and about 75 per cent. of sugars, mostly fructose and glucose, with only traces of other nutrients and no vitamins. However, despite these dismal chemical analyses, honey and maple syrup will continue to be appreciated by all who enjoy pleasant and attractive food.

Cane sugar is much used in food manufactories. Most jams and fruit preserves contain about 70 per cent. of sugar, which acts as a preservative for the fruit. The ingredients of most toffees (candy) are a mixture of sugar, a syrup and a little fat; they may contain up to 70 per cent. of carbohydrate. Boiled ‘ sweeties ’ are often about 90 per cent. cane sugar. Most chocolates are a mixture of 50 per cent. cane sugar and the remainder cocoa-powder.

3. PULSES, NUTS AND SEEDS

This group of foods is a miscellany and includes all the edible seeds except those of the cereal grasses, which have already been considered. Pulses are the seeds of the *leguminosa* family—peas, beans and lentils. The English word *pulse* is taken from the Latin *puls*, meaning pottage or thick pap. The *leguminosæ* are a large family and different species are capable of surviving in very different climates and soils. They are cultivated in almost all civilised parts of the world, so there are very few people to whose diet pulses do not make some regular contribution. The size and nature of this contribution depend in part on the type of pulse that is suited to local agricultural conditions and in part to the nature of the other foods eaten.

In Great Britain, as in other countries with a temperate climate, peas and beans are popular garden crops. They are cultivated by amateurs in their gardens and by professional market gardeners. The crops are harvested before the seed grain is fully mature and dry. Fresh peas and beans contain 65 to 90 per cent. of water and thus resemble leafy and stalk vegetables. The mature seeds of the *leguminosæ*—the dry pulses—contain only 10 to 13 per cent. of water and in this respect, as in many others, closely resemble the cereal grains. All the *leguminosæ* plants make good cattle fodder and so crops may be diverted from human use.

In the tropics a variety of pulses are grown. The seeds are allowed to mature fully and after harvesting and thrashing can be stored dry, like other grain. For good yields tropical pulses require a plentiful supply of water during the early growth of the plant, and then a hot dry period for the final stages of ripening.

In the East, pulses make a much more important contribution to the diet of all classes of society than in the West. So it is proper to consider the role of pulses in Eastern diets first.

TABLE 18, 3. *Pulses (peas, beans and lentils), nuts and seeds (all dry)*

	Range	Selected value	Notes
Moisture, per cent.	8–15	...	...
Cal./100 g.	320–350	340·0	...
Carbohydrate, g./100 g.	55–65	60·0	Soya bean, 20
Protein, g./100 g.	17–25	20·0	Soya bean, 38
Fat, g./100 g.	1–5	2·0	Soya bean, 18. Nuts, usually 40 to 60
Calcium, mg./100 g.	100–200	150·0	...
Iron, mg./100 g.	2–8	6·0	...
Vitamin A, i.u./100 g.	20–200	100·0	...
Ascorbic acid, mg./100 g.	0	0	When sprouted, 10–15
Thiamine, mg./100 g.	0·2–0·6	0·4	...
Riboflavin, mg./100 g.	0·15–0·3	0·25	Soya bean, 0·75
Nicotinic acid, mg./100 g.	1·5–3·0	2·0	...

PULSES IN EASTERN DIETS

The nutritive properties of pulses resemble in many respects those of the whole cereal grains; but there are important differences, which enable pulses to be a valuable supplementary food to cereals and especially to rice.

First, all pulses have a higher protein content than cereals. Most contain about 20 g. of protein/100 g. dry weight. As Table 5, 2 shows, the biological value of pulse protein is not high; but it has been shown in experiments both on rats and on man that a mixture of proteins from rice and pulse is first class, both for maintaining nitrogen balance in adults and for supporting growth in the young: in fact a suitable mixture of rice and pulse proteins may be biologically equivalent to casein. This is an important fact for agricultural planners seeking ways to improve a country's protein supply, since dairy herds take a long time to develop and require a lot of land.

Secondly, pulses as a class are good sources of the B group of vitamins (except riboflavin). More important, the greater part of these vitamins present in the harvested seeds is actually consumed. There are no losses in any way comparable with those that may arise in the milling and cooking of rice. Pulses have therefore a well-deserved reputation as a food which will *protect against beriberi*.

Thirdly, although pulses like cereal grains are devoid of any vitamin C activity, large amounts of ascorbic acid are formed on germination;

sprouted pulses are an excellent *prevention against scurvy.* A recipe that has proved practical and effective in India is described in Chapter 53.

Hospital dietitians in Asia and Africa will find sprouted pulses a useful item for their menus, especially when fresh vegetables and fruits are scarce and expensive. The sophisticated may find them useful at cocktail parties—for guests will like them ; they are cheap, and supplement the nutritive value of the other refreshment.

Soya bean (*Glycine hispida*) is perhaps the most important pulse in the world. It has been a major article of food in China for several thousand years. The whole dry grain contains about 40 per cent. of protein (twice as much as in most other pulses) and also up to 20 per cent. of fat. Soya forms the basis of a great variety of the sauces and pastes with which Chinese cooks garnish their food. To the poor Chinese peasant subsisting on inadequate amounts of rice, the extra protein and fat, and incidentally B vitamins, provided by even a small amount of soya, can be of immense value in maintaining his physiological activities. For the Chinese gourmet, soya is one of the raw materials out of which the cooks create their delicious works of art. The Chinese are great travellers and so have dispersed the food habits of their native land widely. There are few cities of any consequence in the world which do not contain at least one restaurant where excellent Chinese food is served.

Soya beans are now cultivated in many parts of the world, notably in Indonesia, parts of Central Europe and in the U.S.A., but not in the uncertain climate of Great Britain. They are grown in the U.S.A. as cattle fodder.

Enthusiastic food reformers frequently point out the high nutritive value of soya bean for man. Despite this, there appears to be no general appreciation of soya beans in any part of the world outside China. Neither in India nor in Europe are people attracted by the peculiar bitter flavour of soya. This is perhaps because many met it for the first time not in a good Chinese restaurant but when eating some normally well-liked food which had been diluted with soya flour as a measure of war-time economy. A list of British foods into which soya flour crept in war-time would be very long. Soya has frequently suffered from the common psychological reaction to a new food : " It's foreign ; I don't like it."

It seems unlikely that soya beans will ever occupy a position of dietary importance, similar to that which they occupy in China, in any other country. In India, the Middle East, Africa and in many Latin American countries extensive cultivation of the soya bean has been advocated by enthusiasts, sensible of the great value of this food to the Chinese. The task of making the new and strange food acceptable and also of overcoming agricultural problems presents obvious difficulties. Simpler and probably as effective nutritionally is the alternative plan of extending and improving the cultivation of indigenous pulses. Many species exist and these will now be briefly discussed.

Lentils are the seeds of *Lens esculenta* of which many varieties are known. The plants are small, about 25 to 50 cm. high, with small leaves and pale blue flowers. The plant originated in the Mediterranean countries and has been an important crop there for a long time. Esau sold his birthright to his brother Jacob " for bread and pottage of lentiles " (Genesis xxv. 34). Latterly lentils were introduced into India and large areas planted, especially in Bengal. There are several varieties: the Indian and Egyptian kinds are orange-red in colour and these are the lentils most commonly imported into Europe. A green variety also exists. Lentils may be made into soups or ground into a flour.

Dhals.—In India, besides the lentils several other pulses (or dhals) are widely cultivated. The best known are Bengal gram (*Cicer arietinum*), black gram (*Phaseolus mungo*), green gram (*Phaseolus radiatus*) and red gram (*Cajanus indicus*). A pulse, khesari dhal (*Lathyrus sativus*), was once sown widely in Central India. Its special value was that it was very resistant to drought. Even if the main cereal crop failed in a dry season, some khesari could be harvested. However, it was found that if large amounts of khesari dhal were eaten, paralysis of the lower limbs commonly followed. This condition, lathyrism, is discussed in Chapter 33.

GROUNDNUTS (*Arachis hypogœa*), also known as peanuts and monkey nuts, are in fact the seeds of a leguminous plant. They are therefore properly pulses and not nuts. The plants originated in Brazil, but are now grown widely all over the tropics. After flowering, the ends of the flower stalk bend down and the young pods are forced into the ground by the direction of growth. They ripen underground and have to be dug up at harvest.

Groundnuts resemble other pulses in general nutritive value, except that they are rich in fat. The whole seed contains about 40 per cent. of fat, twice the amount in soya beans.

As most children know, peanuts are good to eat, but few would care to eat a lot of them. The cultivation of groundnuts is seldom intended as a primary source of human food. The chief product is the oil, which can be used either as cooking oil or for making margarine and soap. The secondary product is the residue or cake left after the expression of the oil. Groundnut cake is excellent cattle food. It is also in theory an excellent protein-rich food for man. However, it is difficult to overcome the unpleasant taste, which readily causes nausea. Experience has shown that as a diluent of flours from millets, wheat or other sources up to 10 per cent. can be well tolerated; in higher proportions the mixture becomes nauseating and unpalatable.

Modern food technologists have succeeded in making palatable foods, in which a significant proportion of the protein has come from groundnut cake. Unfortunately groundnut products have been found to contain substances which are toxic to poultry (Chapter 25). There is no evidence that groundnuts in the quantities likely to be used for human consumption have any toxic effect on man; however, until more is known about these toxic agents, there will be hesitation in recommending the use of groundnuts or their products on a large scale as human foods.

The Lima bean (*Phaseolus lunatus*), a native of Peru, the cow pea (*Vigna unguiculata*) and the locust bean are other pulses which are widely grown in many parts of the tropics and in subtropical areas.

This list gives only a small selection of a large number of different pulses cultivated in various parts of the world. They all give remarkably similar chemical analyses and have the same general nutritive properties. Like soya bean, small quantities in the diet can (1) significantly increase both the quantity and quality of the total dietary protein, (2) effectively prevent beriberi and (3) (after sprouting) can prevent scurvy.

To sum up : physicians, physiologists and dietitians should strongly recommend the increased cultivation of pulses in tropical areas and especially if there is evidence of protein deficiency or beriberi. The choice of which pulse to grow can be left to the tastes of the inhabitants and the judgment of agriculturists.

Pulses in Western Diets

Pulses are less important in the diets of people in America and Western Europe than in diets in the East and other tropical areas. This is because the greater variety of foods consumed much reduces the risk of protein deficiency or lack of vitamins of the B group. For most people, peas or beans are pleasant foods which can be enjoyed.

The popular garden pea (*Pisum sativum*) is best eaten picked fresh from one's own garden. However, it is now cultivated extensively on a large scale and mostly by mechanical means. Peas have become much more freely available at all times of the year as a result of canning or freezing. The best canned or frozen peas are now as good nutritionally as fresh peas from a garden and taste almost as good.

The common garden bean is the kidney bean (*Phaseolus vulgaris*) or French bean. In France it is known as the Haricot, and in North America as the Bush or Snap bean. It is probably a native of Central America and so can be added to the list of foods acquired by the Old World from the New. There are many varieties. In Britain the beans are sometimes picked when still very immature, and the whole pod sliced and eaten (the *haricot vert* of the French). The popular scarlet runner bean (*Phaseolus multiflorus*) which also originates from tropical America is always eaten sliced in the green pod. Other varieties are grown in which the beans are allowed to mature. They may then be dried. Haricot beans, navy beans and pea beans are names for different varieties. In recent years there has been a great increase in the canning of kidney beans ; the tin (can) of baked beans has become a common article of diet. The broad bean (*Vicia faba*) has been cultivated in Europe for at least 2000 years and is probably a native of Asia. Although very popular amongst amateur gardeners, it is not much grown commercially. Varieties with smaller and less palatable seeds are widely cultivated as cattle fodder.

Digestibility of pulses.—Pulses have a reputation for being indigestible. This was acquired at the time of Galen or even earlier. It is only partially deserved. In health, the digestion of pulses and the absorption of their principal nutrients is practically complete and about as effective as is the assimilation of cereals. However, even in minor gastrointestinal disorders their digestion may be incomplete ; it is often possible to identify with the naked eye fragments of undigested pulses in a loose stool. Only small quantities of well-cooked pulses should be permitted in the diets of patients with alimentary diseases.

Nuts

We know of no record of any people who regularly consumed large quantities of nuts. In Great Britain during the last war it was possible to register as a vegetarian, surrender one's meat ration and receive in return up to 2 lb. of nuts weekly. This quantity of nuts, depending on the species provided, would supply daily at most 500 Cal. This is hardly a large quantity. In 1941 there were only 16,000 registered vegetarians, but the numbers rose to 70,000 by 1947.

However, nuts are an occasional small luxury which everyone enjoys. As the different popular nuts grow in many parts of the world there is a small but flourishing international trade. Most of the imported nuts go straight to the manufacturers of confectionery and biscuits and to bakers.

Most nuts have a high content of fat and protein, but as they are eaten in such small amounts their nutritive value is generally insignificant, compared with their flavouring properties.

Almonds are close relatives of the peaches and plums. They are grown in Great Britain for their decorative blossom rather than for the nuts. Commercial growing takes place in Spain, South France, Italy and California. The almond is used mainly for confectionery and especially as the basis of marzipan. During the last war no one in Great Britain found a real substitute for pounded almonds.

Brazil nuts flourish only in the tropic valleys of the Amazon and the Rio Negro. The nuts grow on very tall trees in the midst of dense tropical forests. Harvesting is a difficult task. Then the nuts have to be ' humoured ' carefully so that they dry slowly and arrive in overseas shops in fine condition just before Christmas.

Cashew nuts were discovered by the Portuguese in South America. Their unique and delicious flavour was quickly recognised. The Portuguese took them to other parts of their Empire. New plantations on the Malabar Coast soon flourished and cashew nuts have remained a characteristic feature of South Indian hospitality for several centuries.

' *Spanish* ' chestnuts are commonly found in many parts of Europe. The nuts used to be eaten extensively by the poor in times of scarcity.

Cobnuts, filberts and hazels are alternative names for the common British hedgerow nut. This is extensively cultivated in Kent and Sussex, but there are also considerable imports from Turkey and Spain. In the South of England nuts should be ready for harvesting on 22nd August, Saint Philibert's day. The nuts have been given a corrupted form of the saint's name.

Pecans are small walnuts grown in the U.S.A. and of high quality.

Pistachios are nuts with green kernels, covered with a purple skin. They are grown in Turkey and Italy and are very expensive, but are used for high-class chocolates and confectionery.

Walnuts are grown in many parts of Europe and in the U.S.A. Walnut trees were known to the classical Greek and ancient Hebrew writers.

The coconut.—This palm contributes to human needs in many ways. As its fruit is not strictly a nut but rather a stone-fruit or loupe, coconuts are a little out of place here. Coconut palms grow on low-lying land often near the sea, and their graceful leaves and the curves of their trunk give great charm to many tropical landscapes. To the hot and thirsty traveller there is no more refreshing drink than the water inside a green coconut and it is also hygienic. However, coconut water is of little nutritive value : it is a minor luxury of the tropics and available to any small boy who can climb a palm unseen by the owner. The white flesh inside the nut, when dried, is known as ' copra.' It has a high content of oil, and coconut oil is the most valued product of the palm. It is widely used as a cooking oil in the tropics and is exported for soap making. The residual cake after the oil has been extracted is known as ' poonac ' and can be used as a cattle food. Copra itself is a good food and can be eaten either dried or fried. It is very rich in fat (over 30 per cent.). Dried coconut is imported into temperate countries and used by confectioners and cake makers, who value its flavour.

The fresh sap of the palm (sweet toddy) is a pleasant drink, but it contains few nutrients. Sweet toddy is readily fermented by yeasts and this product has been the chief alcoholic drink in many parts of the tropics.

SEEDS

Many other miscellaneous seeds play a small part in various diets. On the music-hall stage no Russian peasant is complete unless he is chewing *sunflower seeds*. These have the same composition as groundnuts and are cultivated widely in Russia and elsewhere as a source of oil. Chewing the seeds of these and similar plants no doubt provides an additional small source of nutrients to many peasants.

4. VEGETABLES

There are hundreds of ' common vegetables ' eaten in different parts of the world. Everyone knows what ' vegetables ' are and yet they defy exact classification or description. Some vegetables, like spinach, cabbage and lettuce are leaves ; others—onions, turnips and radishes—are roots ; egg-plants (brinjals or aubergines), gourds and marrows are fruits ; celery is a stalk and cauliflower and globe artichokes are flowers. Clearly there is no biological structure common to ' vegetables ' and largely determining their chemical composition, as in the case of cereal grains.

Nevertheless despite the great variety of botanical structure, vegetables all possess the same general nutritive properties in qualitative terms.

Social Factors

Before discussing the nutritive properties of vegetables it is proper to state that man should eat vegetables because he *likes* them ; vegetables may also be good for him (as innumerable Ministry of Food posters told us during the last war), but this should be a secondary consideration. In the Middle Ages few people ate vegetables regularly. Only the religious houses kept vegetable gardens and these were very poorly stocked. An interest in gardening arose at the time of the Reformation in Europe. It had spread to England in the seventeenth century and to Scotland in the eighteenth. Many new vegetables were introduced, not a few coming from the New World. Both landowners and merchants began to take pride in their vegetable gardens and the produce greatly improved the quality of the table which they kept. The poor quickly followed their example. It was soon demonstrated that a small well-cared-for cottage garden could provide a varied supply of vegetables for a family. English cottage gardeners acquired a well-deserved reputation for their skill as vegetable growers ; any tourist in rural England to-day will see that this skill is still maintained. The same is less true in Scotland.

With the Industrial Revolution many who moved from the country to the town were cut off from their supply of fresh vegetables. To meet the needs of the cities large commercial market gardens were started. There were 559,000 acres of market gardens in Great Britain in 1946. These have been for the most part well run and they continue to produce a great number of excellent varieties of vegetables. However, the marketing of these vegetables has always been unsatisfactory. Some delay in the passage of the vegetables from the market gardens to the greengrocers' shops in the cities is inevitable. This may be extended, sometimes to days, by a complicated trade with too many middlemen. As a result the urban housewife may find in the shops a selection of partly spoiled vegetables at prices beyond her reach. In many urban homes the habit of eating vegetables regularly has not been acquired ; this is often attributed to ignorance, whereas a more important cause is the poor quality and excessive price of many vegetables. In the past, many housewives had neither the facilities nor the skill necessary for preparing and cooking vegetables. Families can hardly be blamed if ' they don't like vegetables.' In the last decade the position has greatly improved as a result of the increase in the quality and quantity of good canned or frozen vegetables. Here the food industry of the U.S.A. has led the way. In Great Britain we still have much to learn about the canning of vegetables and also about the marketing of fresh supplies. In the tropics a beginning has hardly been made in solving these problems.

A regular supply of good vegetables, either fresh or canned, should be an essential part of good living and good feeding. Vegetables add to the elegance and attractiveness of a meal. There is no reason why they should be beyond the financial means of any family living above the poverty level.

NUTRITIVE PROPERTIES OF VEGETABLES

These are shown in Tables 18, 4 and 18, 5.

TABLE 18, 4. *Vegetables :* (a) *Green, leafy*

Cabbage, brussels sprouts, lettuce, spinach, parsley, amaranth, coriander, fenugreek, neem, etc.
(Composition in terms of the retail weight, as purchased.)

	Range	Selected value	Notes
Moisture, per cent.	75–80	...	...
Cal./100 g.	10–50	20·0	...
Carbohydrate, g./100 g.	1–12	3·0	...
Protein, g./100 g.	1–4	2·0	...
Fat, g./100 g.	Trace	0	...
Calcium, mg./100 g.	25–500	100·0	In temperate zones, 75 In tropical zones, 250
Iron, mg./100 g.	1–25	5·0	...
Vitamin A, i.u./100 g.	1000–10,000	3000·0	In the higher range in the tropics
Ascorbic acid, mg./100 g.	10–200	50·0	In temperate zones, 30 In tropical zones, 180
Thiamine, mg./100 g.	0·03–0·08	0·05	...
Riboflavin, mg./100 g.	0·03–0·25	0·08	Kale and spinach up to 0·5
Nicotinic acid, mg./100 g.	0·2–1·0	0·5	...

TABLE 18, 5. *Vegetables :* (b) *Others*

Onions, turnips, cauliflower, leeks, egg plants, pumpkins, gourds, etc.
(Composition in terms of the retail weight, as purchased.)

	Range	Selected value
Moisture, per cent.	70–90	...
Cal./100 g.	10–50	25·0
Carbohydrate, g./100 g.	2–10	5·0
Protein, g./100 g.	0·5–2·5	1·5
Fat, g./100 g.	0–0·4	0
Calcium, mg./100 g.	20–100	65·0
Iron, mg./100 g.	0·5–4·0	1·5
Vitamin A, i.u./100 g.	0–300	150·0
Ascorbic acid, mg./100 g.	5–100	25·0
Thiamine, mg./100 g.	0·05–0·20	0·07
Riboflavin, mg./100 g.	0·01–0·20	0·05
Nicotinic acid, mg./100 g.	0·1–1·0	0·5

It will be seen that the value of vegetables as a source of energy is almost negligible. Most will provide from 10 to 50 Cal./100 g. To obtain 1000 Cal. it would be necessary to eat 4 to 5 lb. of vegetables. The large bulk of vegetables helps to promote satiety, and this, with thei low-calorie value, makes them useful in the prevention and treatment of obesity. Vegetables are also of insignificant value as a source of proteins and essential amino acids. All vegetables contain indigestible cellulose fibre. This increases the bulk of the fæces and is a useful property. Constipation is extremely common in sedentary urban populations since milling processes remove much of the roughage from cereals. Vegetables, by increasing the size of the stool, have a mild and beneficial laxative effect.

Most vegetables contain amounts of calcium and iron that are probably physiologically significant. However, it is doubtful if the actual figures given for these minerals in food tables are of much value. The mineral content of different samples of the same vegetable may vary greatly. The uncertainties attending the absorption of these elements from the alimentary canal have already been discussed (Chapter 11). They make it difficult, if not impossible, to assess whether the calcium in vegetables can be utilised by young children for the growth of bones. But many green leafy vegetables are very rich in calcium and it would be reasonable to suppose that in the normal diet of a child some would be available for growth.

Even though much of the iron present in vegetables may not be absorbed, the ascorbic acid which they also contain may aid its absorption (p. 175).

All vegetables contain small amounts of the B group of vitamins, but their contribution to the total intake is seldom great. Most leafy vegetables are fair sources of riboflavin. In the tropics it has often been found that a small supply of greens will reduce the incidence of angular stomatitis and other mucocutaneous degenerations, often attributed to an insufficiency of riboflavin.

The chief nutritive value of vegetables is the supply of carotene (the precursor of vitamin A) and of ascorbic acid. Cereals and pulses are in general totally devoid of both these vitamins. The exceptions to this are few and minor. So vegetables are able to make good two of the major deficiencies likely to arise on diets containing excessive amounts of cereals. It is in this way that vegetables *balance* a diet.

The carotene content of vegetables is very variable. The great majority have good vitamin A activity. There is a rough relation between colour and carotene content. All green leafy vegetables are rich and some, such as kale, very rich (vitamin A potency 8000 i.u./100 g.). Carrots are exceptionally rich and may contain double this amount. Cucumber, cauliflower, some of the gourds and other pale vegetables may contain very little.

All vegetables contain valuable amounts of ascorbic acid, but the quantities are variable and losses in cooking and preparation may be great. However, a single helping of vegetables (3 oz.: 90 g.) daily, even if it has been badly treated by the cook, will usually provide at least 10 mg. of ascorbic acid, an amount known to prevent scurvy. The losses of vitamins in cooking and preserving are discussed in more detail in Chapter 22.

In many tropical countries it is impossible to over-emphasise the improvement in health that is likely to arise from even a small increase in the vegetable supply. A poor anæmic woman with insufficient iron, vitamin A and ascorbic acid in her diet may find immeasurable improvement in her health as a result of taking one helping of good garden vegetables a day. In Africa and Asia there are a few keen and competent gardeners; some are schoolmasters who set an excellent example to their pupils, but their numbers are few in relation to the need. A single enthusiast in a village or small town, by giving instruction and encouragement to his neighbours in the art of gardening, can carry out first-class preventive medicine in his spare time. He can do this alone in the manner he likes and he will not be dependent on the help of the government, the United Nations or any expert committees, though these are available to provide any advice that he needs.

There are three other types of 'vegetables' which may serve as food for man, and so deserve brief mention.

Seaweed and several kinds of marine algæ have been used as a human food by the Chinese for many centuries and to-day seaweeds are eaten regularly in significant amounts by several Japanese communities. Carrageen 'moss' is a seaweed still eaten on the west coasts of Scotland, South Wales and Ireland. As already described (p. 51), agar and alginic acid are polysaccharides derived from seaweeds which are used by housewives and food technologists to alter the texture and consistency of foods, especially in making jellies.

The chief carbohydrates in seaweeds are mannitol and the polysaccharides alginic acid and laminarin. Nothing is known of their digestibility. There are small quantities of cellulose present. Seaweeds contain less than 1 per cent. of fat, but appreciable amounts of protein, though little is known about their biological value. All seaweeds have a very high mineral content and are said to contain all the minerals known to be physiologically essential for man. A fuller account of the nutritional properties of seaweed with a bibliography is given by Black (1953). There are several million tons of seaweed round the shores of the British islands that could be harvested. So far attempts to make a palatable food have met with little success. Seaweed is used as a fertiliser and in the manufacture of iodine.

Fungi.—Ramsbottom (1953) has given a good account of the use of mushrooms and toadstools as food. The British appear to be uniquely conservative in their fear of toadstools. Only certain species are poisonous, notably the Death Cap (*Aminita phalloides*) which has been responsible for nearly all the deaths. Many British toadstools are excellent eating.

On the continent and in the tropics a great variety of fungi are eaten. Fungi are for the most part delicious food and are eaten for their flavour. As they only contain up to 3 per cent. protein, less than 1 per cent. fat and not more than 2 per cent. carbohydrate, their nutritive value is negligible, except perhaps for the unknown vitamins and antibiotics they contain and the fat in which they are often fried.

Fungi are valuable as one of the few luxury foods that are freely available to poor countrymen. With the increase in commercial cultivation they are also becoming available at cheaper prices in the cities. They are much appreciated by all who love good food and have good digestions.

5. FRUITS

Since the beginning of civilisation men of ingenuity who have had a little land to spare have used it to cultivate orchards and fruit gardens. In this art there has been a steady and progressive increase in skill and technical knowledge. The modern grower can provide fruit of great variety and excellent quality. Table 18, 6 shows the development of fruit growing in Great Britain.

TABLE 18, 6. *Origin of some British cultivated fruits*

Fruit	Date of introduction	Origin
Apples and pears	Roman times	Europe
Cherries	A.D. 100. Improved varieties planted in Kent, 1540	Flanders
Apricots	Sixteenth century	Asia Minor
Figs	Sixteenth century	Mediterranean
Grapes	Sixteenth century	France
Mulberries	Sixteenth century	Central Asia
Plums	Sixteenth century	Italy
Peaches	Sixteenth century	Southern Europe (from China)
Quince	Sixteenth century	Southern Europe (known to the Greeks)
Strawberries	Seventeenth century	Virginia
Damsons	Unknown	Damascus
Currants and gooseberries	Seventeenth century	Near East
Loganberries	1897	U.S.A.

Raspberries and blackberries are natives of Great Britain.

No other class of foods has such a variety of pleasant and attractive flavours. These are provided by organic substances which for the most part remain unidentified. By their delicacy of colouring, fruit attracts the eye as well as the palate. For thousands of years vintners have been preserving the best and most delicate flavours in wines and liqueurs. Housewives have been similarly engaged for about three hundred years in preserving and jam making. In the last hundred years they have been greatly assisted by food technologists. All these skills have contributed beyond measure to the pleasures of the table and the art of living.

TABLE 18, 7. *Fruits* (*fresh or canned* *)

Apple, raspberry, orange, peach, mango, tomato, papaya, banana, etc.
(Composition in terms of retail weight as purchased.)

	Range	Selected value	Notes
Moisture, per cent.	75–90	...	...
Cal./100 g.	20–80	50	...
Carbohydrate, g./100 g.	2–20	10	...
Protein, g./100 g.	0·2–2·0	0·5	...
Fat, g./100 g.	0–1	0·5	...
Calcium, mg./100 g.	5–40	20	...
Iron, mg./100 g.	0·1–1·0	0·3	...
Vitamin A, i.u./100 g. (as carotene)	0–3000	400	Mango 1000–2500 Tomato 1000–3000 Orange 150–200
Ascorbic acid, mg./100 g.	0–300	30	Very variable
Thiamine, mg./100 g.	0–0·1	0·04	...
Riboflavin, mg./100 g.	0–0·1	0·05	...
Nicotinic acid, mg./100 g.	0·2–1·0	0·4	...

* Canned fruit often contains added sugar.

The nutritive value of fruits is much less important. The only essential nutrient in which fruits are rich is ascorbic acid. Almost all fruits contain physiologically significant amounts of this vitamin and some are very rich. As fruits are often eaten raw, large intakes of the vitamin may be provided. Table 14, 1 gives the ascorbic acid content of some fruits. How important fruit is in a national dietary depends on one's opinion as to man's requirements of ascorbic acid. This has already been discussed in Chapter 14. Personally we are unconvinced of the desirability of maintaining the tissues saturated with ascorbic acid. Though we welcome the modern American habit of taking tomato juice for breakfast—for it is a delicious drink—we are not satisfied that the custom ordinarily makes any important contribution to better nutrition. Cannot we be allowed to enjoy something without first having to prove that it is good for us ?

Fruits, of course, like vegetables contain cellulose which is indigestible and so adds bulk to the stools ; fruits are thus mild natural laxatives. For this reason a few people with sensitive colons can take fruit only in very small quantities ; if larger amounts are taken diarrhœa follows.

The polysaccharide pectin present in fruit has been described in Chapter 4. It assists in the formation of jellies and is of great value to jam-makers.

Most fruits contain small quantities of carotene and the B group of vitamins. The amounts present are not usually sufficiently great to increase significantly the intake of these nutrients by people who are already living on a good mixed diet, but under certain circumstances they may be very valuable. In many parts of the tropics there is a sudden and obvious improvement in the health of the children coincident with the mango or jack-fruit season. Children may eat enormous quantities of these fruits.

Fruits contain little or no protein or fat. Most contain 5 to 20 per cent. of carbohydrate. Ripe fruits contain no starch. Fructose and glucose are the chief sugars found. These two sugars are often present in equal proportions. Apples and pears contain much more fructose, while apricots and peaches contain sucrose.

Fruits contain a great variety of organic acids. These have already been referred to on page 150. They are responsible for the sourness of unripe fruit. During ripening the concentration of these acids falls and that of the sugars rises. As already described, the body readily disposes of these acids ; most are easily oxidised, some excreted in the urine and a few are not absorbed from the gut. They do not give rise to acidosis : indeed the consumption of fruit usually leads to an alkaline urine, because most fruits contain more sodium and potassium than phosphorus or sulphur.

Bananas are a fruit which requires special mention. They contain much larger amounts of carbohydrate than most fruits and so can act as a useful source of energy. There are about fifty varieties of bananas. They vary widely in composition, but may contain carbohydrate 20 g., protein 1 g., fat 0·2 g. with a caloric value of about 80 Cal./100 g. In some parts of the tropics they may be the staple food of children and are often eaten together with large amounts of cassava. In this way large amounts of carbohydrate may be eaten with only very small quantities of protein. Evidence of protein deficiency (kwashiorkor) is frequently found in children in Africa who eat large amounts of bananas.

The staple diet of Buganda is matoke (*Musa species*), a banana usually eaten green. This contains a high concentration of serotonin (Crawford, 1962). Matoke eaters may excrete 20–100 mg. of 5-hydroxyindolyl acetic acid in their daily urine. In controls the daily excretion is less than 7 mg. If 5-HIAA excretion can be taken as a measure of circulating serotonin, the matoke-eating African may be subjected to a considerable cardiovascular stress. This might be in part responsible for the endomyocardial fibrosis which is common in Buganda and neighbouring countries.

In small quantities bananas are a pleasant and attractive food and have acquired a well-merited reputation in temperate climates. They are very easily digested. Ripe bananas contain little or no starch ; the carbohydrate is present chiefly as sucrose, fructose or glucose. It is important that bananas given to children be fully ripe. They can be digested by babies as early as the third month. They are also useful for children with diarrhœa and for adults with sprue or indeed with any disease of the alimentary tract. Bananas are also a useful food for convalescence after any severe illness.

The effects of various methods of preserving fruit (canning, drying, freezing, etc.) are discussed in Chapter 22.

CHAPTER 19

MEAT, FISH AND EGGS

1. MEAT AND MEAT PRODUCTS

IN Chapter 5 it was pointed out that there is no evidence that any protein of animal origin is essential for man. Indeed this fact has been amply demonstrated by many vegetarians who have led full and active lives, involving much expenditure of physical energy. At the same time it was said that as soon as a family or community achieves some measure of success in the struggle for existence above the poverty level, there is nearly always an increase in the amount of meat they consume. Meat consumption is closely correlated with income. Although higher standards of living are often associated with better health, this is not necessarily attributable to a larger consumption of meat. Other factors are associated with higher incomes and may affect health.

THE QUALITY OF MEAT

The great majority of mankind have a natural appetite for meat. The flesh of more than one hundred different species of animals is regularly eaten by man. Of course there are very great differences in the quality of these ' meats,' as judged by the prices that they can command in a restaurant. The reputation which most 'meats' have acquired is not closely related to their nutritive value, as found either by chemical analyses or feeding trials.

Lean muscle from most species contains about 18 per cent. of protein and 1 per cent. of fat, another 1 per cent. is mineral ash and the rest water. ' Meat ' as sold by the butcher may contain—in addition to muscle—10 to 50 per cent. of fat. There are thus great variations in the fat content of cuts from different parts of the same animal and also in those from other animals of the same species, depending on their previous nutrition. The variable amounts of fat in meat make great differences in its caloric value. The use of food tables for calculating the energy content and protein content of diets containing much meat is subject to large errors.

DIGESTIBILITY OF MEAT

The presence of large quantities of fat in a meal is well known to cause delay in emptying the stomach. All cuts of pork usually contain large amounts of fat and this probably explains why pork has acquired the reputation of being indigestible. Similarly salmon, herring and other fat fish are supposed to be poorly digested. In fact, both the protein and the fat in flesh food are readily digested and absorbed, only small amounts being discarded in the fæces. They may, however, contribute to dyspepsia in patients who are so disposed for any reason.

In addition to muscle cells, all meat contains some fibrous connective tissue and fascia. These contain collagen from which gelatin is obtained on boiling. This fibrous tissue is not so readily digested as muscle protein and also makes the meat tough to chew. Muscle from older animals contains more fibrous tissue and so is generally tougher.

When meat is hung for some time, sarcolactic acid and other acids develop; these facilitate the gelatinisation of fibrous tissue and so make the meat softer. The flesh of animals that have been hunted is reputed to be superior to that of those slaughtered at rest. This has been attributed to the beneficial effects of the large amounts of lactic acid formed just before death.

The nature of the flavours of meat is little understood. They may be associated with those readily soluble substances the meat 'extractives,' which are used for making beef teas and similar preparations.

Thus the factors that are responsible for the quality of good meat are but little understood either by the chemist or the biologist. Butchers and stockmen have little scientific knowledge of how to produce these qualities; indeed the whole subject is surrounded by a *mystère*, as a brief conversation with any stockman will show. Housewives and the general public are for the most part conservative and prejudiced. This can be seen in the strong emotional reactions often provoked by any new type of meat, as for instance the introduction of whalemeat into Great Britain during the last war.

Physicians have contributed to the confusion and superstition. Many textbooks of medicine have insisted until quite recently on the superior quality of *white* meats (poultry and game) in contrast to the inferior *red* meats (beef and mutton) especially for invalids and convalescents. The superiority of white meats has never been satisfactorily demonstrated. It is a myth.

Nutritive Properties of Meat

Meat is, of course, of particular value because it contains protein of high biological value. It is also important as a source of energy, more especially if it contains large amounts of fat.

Meats are usually rich in iron and also in phosphorus, but contain little calcium. They are an important source of nicotinic acid and riboflavin. Indeed in most British and American diets about half the total nicotinic acid and one quarter of the total riboflavin come from meat. Meats also contain some thiamine; pork contains the most. There is very little vitamin A in animal fats, except those from the liver. Although the content of ascorbic acid in fresh meat is low, and some of this may be lost in cooking, it may be sufficient to protect against scurvy. The

TABLE 19, 1. *Meat and meat products*

(Composition in terms of the retail weight, as purchased.)

	Range	Selected value	Notes
Moisture, per cent.	40–80	...	...
Cal./100 g.	100–400	250	...
Carbohydrate, g./100 g.	Negligible	0	Liver, 1–5
Protein, g./100 g.	10–30	20	...
Fat, g./100 g.	5–40	20	Very variable
Calcium, mg./100 g.	8–20	12	...
Iron, mg./100 g.	1–8	4	Liver, 6–14 Blood sausage up to 20
Vitamin A, i.u./100 g.	0–100	40	Liver up to 45,000
Ascorbic acid, mg./100 g.	Negligible	0	...
Thiamine, mg./100 g.	0·05–0·30	0·10	Pork, 0·7
Riboflavin, mg./100 g.	0·1–0·3	0·15	Liver and kidney, 0·7–3·0
Niacin, mg./100 g.	2–6	4	Liver and kidney, 5–15

Arctic explorer Stefansson and one of his assistants lived for a year on a diet of animal protein, mainly meat, and maintained good health (McClellan and DuBois, 1930).

OFFAL

This curious word—a corruption of off-fall—is used to describe those parts of an animal that are not good butchers' meat. Offal includes liver, kidneys, pancreas (sweetbread), heart, blood, lungs (lights) and intestines (tripe). Offal, though of poor ' quality ' from the butchers' point of view, is for the most part of good nutritional value. The liver contains more vitamins and absorbable iron than muscle and so is an especially valuable food. At one time the consumption of half a pound of lightly cooked liver each day was the only means of saving the lives of patients with Addisonian anæmia. Dietary liver has been gradually replaced, at first by injection of liver extracts, and now by vitamin B_{12}. Liver nowadays plays a very small part in hospital dietetics. Liver, kidney and pancreas, being rich in cells, contain more nucleic acids than muscle. For this reason patients with gout have been advised to avoid them. Brain contains large amounts of lipids and especially phospholipids. In a pre-scientific age it acquired a quite spurious reputation as a food for the intellect.

Haggis is, of course, offal. The essential ingredients are the liver, heart and lungs of a sheep. These are minced and added to oatmeal with a little onion, pepper and other suitable herbs and spices. All this is packed into a sheep's stomach and steamed. Turnips and whisky are the proper accompaniments. The visitor to Scotland who is lucky enough to be given haggis in a traditional Scottish home will enjoy a delightful meal.

Black pudding is another traditional Scottish food based on offal. It is a mixture of blood and oatmeal.

Pâté de foie gras is *strictu sensu* classified as offal ; this luxury food is made from the livers of geese which have been kept in strict confinement and forcibly fed to excess for several weeks. It properly comes from Alsace and is delicious.

Sausages have been used throughout historical times as a convenient form in which meat can be preserved and transported. Odysseus, waiting to revenge himself on the suitors, sat impatiently like " a man before a great fire taking a sausage full of fat and blood, turning it this way and that and longing to have it roasted more speedily." Cities like Oxford and Cambridge, Bologna and Hamburg have achieved fame from their sausages as well as from their universities. The basis of all sausages is a mixture of meat and bread and their quality depends on the proportion and quality of the meat. In Great Britain the best sausages contain pork and the cheaper varieties beef. During the last war it was compulsory to substitute soya flour for part of the meat.

Germany has a great reputation for the variety of its sausages, many made from liver and offal. A variety of seasonings are used ; chipolato sausages contain chives ; saveloys, pigs' brains. With such varied recipes, any general statement of the nutritive value of sausages would be liable to a large error. In the absence of any precise knowledge of the composition, protein 12 g., fat 20 g., carbohydrate 12 g. and Cal. 280/100 g. is a reasonable estimate.

MEAT EXTRACTIVES, BEEF TEA, SOUPS, ETC.

Meat extracts have been used for generations and some, like Liebig's famous extract, have been much studied by physiologists in the past. Such extracts contain the freely water-soluble contents of muscle—potassium, phosphates, peptides, nucleotides, creatine, vitamin B_{12} and other vitamins. The juice that is formed as a by-product in the great meat-canning factories in the Argentine and the U.S.A. is dried and sold as Bovril, Oxo and other beef extracts. When reconstituted with hot water, the ' beef tea ' formed has a very low concentration of solids. They do not supply significant amounts either of calories or protein, so they are not true ' foods.' However, beef teas may have a place in dietetics since they stimulate appetite and hence may be useful in the feeding of convalescents. Whether the stimulus to appetite is some specific chemical substance in the extracts, or just an attractive flavour and smell, is uncertain. For similar reasons, it is physiological to begin a large banquet with a clear soup.

' SLUGS AND SNAILS AND PUPPY-DOGS' TAILS ' OR ' CHACUN À SON GOÛT '

Those of us who have been brought up as members of one of the great religions of the world—particularly caste Hindus, but to a lesser extent all Mohammedans, Jews and Christians—seldom realise the extent to which our daily diet is artificially restricted. Religious taboos are partly responsible, but custom and tradition are much more important. There are many foods which would cause any ‘ civilised ’ man to revolt at the very thought of eating them ; yet some of these foods are very palatable and many are nutritious. They can play an important part in the diet of unsophisticated people. Nicol (1953) has recorded how the Isoko tribe in Nigeria may obtain up to 20 g. of protein/head/day from mud-fish, monkeys, pangolin, porcupine, cane-rat, Gambian rat, snails, palm weavils and frogs. Without the addition of these luxuries to their diet, the Isoko would be very poorly off. Young boys show much ingenuity in hunting and trapping such animals.

Bristowe (1953) gives an interesting account of the insects that may be eaten in Indo-China and Thailand. Even wealthy and well-bred people consider the larvæ of a coffee-boring moth (*Zeuzera coffeæ*) delicious when roasted and eaten with rice and salt. Bristowe has made an impressive list of insects known to be appreciated by man. Properly cooked and served, locusts can be an attractive and nourishing food. Flying ants cooked in butter are considered to be a delicacy in certain parts of Africa.

On a visit to a famine area in South India, one of us (R. P.) observed that the outcast children were in a much better state of health than the children of the caste Hindus. Careful questioning provided the information that these children were accustomed to hunt and eat frogs and rats—a pastime prohibited to high-caste boys.

Many South Americans rear guinea-pigs, especially for the table, and they are reputed to be very tasty. This practice seems particularly revolting to laboratory-trained nutritionists.

There are many records of the inhabitants of besieged cities in Europe eating cats, dogs and even rats with avidity. Man’s range of foods is much wider than social circumstances normally permit. Amongst primitive people these foods may contribute significantly to the total protein content of the diet and so improve health—particularly of small boys. A visiting nutritionist may well fail to be informed about these foods, unless special enquiries are made. Few of these foods have been analysed and little is known about their nutritive value.

It has been stated that the inhabitants of certain parts of Africa would be better off nutritionally if the wild animals were exterminated and the grazing lands used for cattle, sheep and goats. This view is now being challenged. Pirie (1962) quotes figures showing that the yield of meat from game such as blestock, eland, wildebeest, springbok, if properly protected and culled, is likely to be greater than that obtained from domestic animals grazed on the same land. He also discusses the possibility of hippopotamus-farming in swamps.

2. FISH AND OTHER SEA FOODS

Fish are an important source of animal protein for many people. Lean fish contains less than 1 per cent. of fat and about 10 per cent. of protein with caloric values ranging from 50 to 80 Cal./100 g. The common lean fish on the British coast are cod, haddock, pollack, saithe, brill, ling, whiting, John Dory, lemon sole and turbot. These fish have a reputation—for the most part well merited—as being a ' light ' and easily digested food, suitable for invalids. Fat fish contain 8 to 15 per cent. of fish oil and so have a higher caloric value than lean fish—80 to 160 Cal./100 g. Fat fish eaten in Great Britain are herring (including the preserved forms, kippers and bloaters), pilchards, salmon, whitebait, eel, sardines and sprats. Intermediary species—usually with 2 to 7 per cent. of fat—are hake, halibut, mackerel, mullet and trout.

Fish proteins have a high biological value similar to the proteins of land animals. Yet, although many fish are delicious, on the whole, fish are less tasty than meat, and a fish diet tends to be monotonous. Good cooks have a great variety of sauces and garnishes by which they make fish more interesting and appetising. In the Middle Ages, housewives used the herb garden with skill to flavour the flesh of coarse fish such as carp, pike, perch, roach, dace and chub, which came out of the fishponds kept by the great manor houses. The monosyllabic names of these fish indicate that they were familiar to the earliest users of the English language. The art of cooking them is now all but lost. Too few anglers' wives have the skill to make these fish palatable.

The content of protein in fish is somewhat less than in meat and there is often a large waste in the scales and bones. This should be remembered in calculating the relative cost of proteins of different origin.

The only fish offal commonly eaten is the roe, both the hard roe and the soft roe or milts. Cod roe and herring roe contain 20 to 25 per cent. of protein and are rich in nucleic acids. True caviare is the roe of the sturgeon ; many imitations are produced by colouring other fish roes. This rich and tasty food contains about 30 per cent. of protein and 20 per cent. of fat.

Fish oils are rich sources of the fat-soluble vitamins, but otherwise fish do not contain important amounts of either vitamins or minerals, except that small fish—such as sprats and sardines—may be a useful source of calcium when eaten whole, together with the bones. In the great river deltas of the East, where there is extensive cultivation of rice (a cereal poor in calcium) and few or no dairy cattle, the general level of calcium intake is always low. This can be improved by proper use of the small fish which abound in the ditches, tributaries and irrigation canals that lead off from the big rivers.

Lobsters, *crayfish*, *crabs*, *shrimps* and other crustaceans have little fat and an energy value of about 50 Cal./100 g. They are very tasty. But the coarse, big muscle fibres of the larger species are not easily digested.

Some people are sensitive to the proteins of these creatures and develop a variety of allergic reactions from eating them.

Oysters, cockles, mussels, clams, scallops, whelks, winkles and other molluscs contain rather more protein (15 per cent.) than most fish. They also contain about 5 per cent. of the carbohydrate glycogen, but little fat. Many people find them very good eating. Oysters have acquired a reputation as an expensive luxury food, whereas the other molluscs are often regarded as poor man's fare ; all can be attractive and useful foods.

These shellfish live on seashores and are sometimes gathered near the output of urban sewage. Unfortunately they easily harbour bacteria, particularly those of the Salmonella group. Proper supervision is necessary both of sewage disposal and the collection of shellfish, to prevent the danger of infection. Though shellfish such as mussels and winkles are safe if properly cooked, it is well to be sure that those eaten raw—such as oysters—come from a pure source.

The Roman snail (*escargot*), though a land animal, may be mentioned here. It was highly esteemed by the Romans who introduced it into many parts of Europe including Great Britain. Obviously it has not travelled far in 2000 years, because its present distribution is largely confined to areas of Ancient Roman occupation. The *escargot* is one of the glories of the modern French cuisine.

Cuttlefish, squid and octopus are eaten by maritime peoples in many parts of the world. Little seems to be known about their nutritive value.

The sea cucumber (*bêche-de-mer, cucumaria*) is a holotharian worm regarded as a delicacy by the Chinese and eaten by them wherever they have settled. Many other races are less enterprising in their use of invertebrates as a source of food.

An increase in the consumption of sea food requires improved methods of conservation. Many offshore waters—notably the North Sea and the waters around Iceland and the Faroes—have been overfished. Very rich fishing grounds are available in deeper and less accessible waters ; though in many parts of the world such as Africa and South-East Asia the traditional methods of fishing—the nets and the boats—are ill-adapted for exploiting these fields. Recently modern methods of fishing with motor trawlers and drifters have been greatly extended in tropical seas. The supply of fresh-water fish can be increased by systematic cultivation with proper stocking and the use of mineral and nitrogen fertilisers added to the fishponds. Some progress along these lines has been made in the tropics, often stimulated by the Fisheries Divisions of FAO. The possibility of 'cultivating' the Scottish lochs has been investigated, but apparently is not an economic proposition.

3. EGGS

Since the egg forms a complete food for the embryo chick, it is naturally rich in essential nutrients. An average hen's egg, weighing about

2 oz. or 60 g. contains 6 g. of protein and 6 g. of fat and yields about 80 Cal. The proteins—most of which are albumins in the white of the egg—are of high biological value. A hen's egg contains about 30 mg. of calcium and 1·5 mg. of iron. The yolk is a rich source of vitamin A and also contains significant amounts of thiamine, nicotinic acid and riboflavin. There is little or no ascorbic acid. The eggs of many other species of birds are eaten in various parts of the world and all have approximately the same nutritive value as the egg of the domestic hen. In Great Britain plovers' eggs were once a Royal delicacy but, wisely, they are now an illegal article of trade because modern methods of agriculture destroy the nests ; so the lapwing (*Vanellus vanellus*) is now a ' protected ' bird. On the other hand the herring gull (*Larus argentatus*) is a predatory and rapidly increasing species whose numbers might be kept in check by a larger consumption of its eggs.

Eggs may be eaten in many ways. They are widely used in cooking, including the making of cakes. Many artificial egg powders (' custard powders ') are on the market. Yellow colouring matter may give the appearance of eggs, but such substitutes have not the same nutritive value.

CHAPTER 20

MILK AND MILK PRODUCTS—OILS AND FATS

1. MILK AND CHEESE

MILK is the sole natural food of the human infant for the first few months of life. After about 3 to 6 months it is desirable to give supplementary foods and gradually wean the infant on to a good mixed diet. In this process milk slowly loses its dominant place in the infant's diet, but for the first two years of life it is important that milk should remain the largest single item of food.

It is possible to raise infants satisfactorily on modified cow's milk from the moment of birth. But clinical experience indicates that under most circumstances human milk is the most suitable food for infants, at least for the first few months of life. However, there is now good evidence from a controlled study in Sweden (Mellander *et al.*, 1959) that babies can be reared on cow's milk preparations and be in every respect as healthy as breast-fed babies. Artificially fed babies are often bigger than breast-fed babies, but it is not known whether this is advantageous or not. It is customary in Western homes to advise the weaning of infants between 6 and 9 months. This is probably good advice when a suitable supply of cow's milk is available. But it may be disastrous in those parts of the world where fresh cow's milk is not available. In such circumstances lactation must be prolonged. Fortunately there is no doubt that healthy, well-nourished mothers can give their children sufficient breast milk to supplement adequately a mixed diet devoid of cow's milk for up to 2 years, without damage to their own health. It is well established that from the age of 2 and until growth ceases, children will grow more rapidly and reach maturity sooner if given ample quantities of milk. Increased growth rates are generally associated with improved child health and vitality and with relative freedom from disease. All nutritionists would agree that a regular intake of milk is beneficial to growing children. There are, however, many people who have doubts as to whether excessive quantities (more than 2 pints or 1 *l.* daily) are desirable. It is not proven that the unusually rapid growth promoted by such large intakes is beneficial. Nor is it necessarily desirable that full growth should be completed at an early age. It is well established in rats that the life span can be lengthened by delaying the onset of maturity by dietary means (see Chapter 57). Is it possible that very large milk intakes—by accelerating the growth of children—may ultimately shorten their lives ? There is no evidence as yet to substantiate these fears. Nevertheless there are real doubts about the advisability of giving children unlimited amounts of milk.

Widdowson and McCance (1954) have shown that children can grow well on a diet composed almost entirely of wheaten bread and vegetables, with no milk. This evidence should remove any despair from the minds of those responsible for the care of children who have no access to dairy herds. But it should not be used as an excuse for failure to work for an agricultural policy designed to develop dairy herds for the future.

As a complete food easily given, readily digested and absorbed, milk is an ideal food for invalids, especially for patients with acute illnesses. There is no evidence, however, that milk is an indispensable food for adults. As a good source of the principal nutrients it can be recommended for those who like it. Because of the high content of short-chain fatty acids in milk fats, it is probably advisable for adults to limit consumption to not more than 1 pint daily. Kon and Cowie (1961) have edited an admirable book in two volumes. This covers all aspects of the nutritive value of human and dairy milks and the physiology of their secretion.

Chemical Composition of Milk

The essential chemical constituents of human milk and the milk of some other species are set out in Table 20, 1. The figures for human milk are mostly derived from the thorough study carried out in Great Britain by Kon and Mawson (1950). But studies in the U.S.A. (Macy, 1949), Johannesburg (Walker *et al.*, 1954), Nigeria (Jelliffe, 1952) and in India (Gopalan, 1958) all show that although there may be wide variations in the nutrient content of individual samples of human milk, the general picture is the same throughout the world. Except for its vitamin content, the composition of human milk appears to be largely independent of the state of nutrition of the mother. Even after prolonged lactation for 2 years or more, the quality of African women's milk appears to be well maintained, though the quantity produced may be small.

Severely undernourished women in times of famine often manage to feed their babies surprisingly well.

The proteins are perhaps the most important nutrients in milk. The principal protein is caseinogen ; but lactalbumin is also important ; in human milk it provides about half the protein, though only about one-fifth of the protein in cow's milk. Milk also contains about 40 to 80 mg./100 ml. of non-protein nitrogen (Hytten, 1954). The biological value of milk protein is very high. It will be observed in Table 20, 1 that human milk usually contains less than half as much protein as cow's milk. For this reason cow's milk should be diluted before feeding it to very young infants. About 20 per cent. of the caloric value of cow's milk is provided by protein, as compared with only 6 to 7 per cent. in human milk. As judged by the standards set out in Table 5, 3, human milk is thus a poor source of protein. The small quantity of protein in human milk is evidently most efficiently utilised.

Gyorgy (1954) has shown that human milk contains an essential

TABLE 20, 1. *Typical analyses of milk from various species*

(All values in g./100 ml.)

	Carbohydrate	Protein	Fat	Calories
Human . . .	6·8 (6·2–7·6)	1·5 (0·6–2·0)	4·0 (2·0–6·2)	68
Cow . . .	5·0 (4·2–6·8)	3·5 (2·5–4·0)	3·5 (3–6)	66
Buffalo . . .	4·5	4·3	7·5	103
Goat . . .	4·5	3·7	4·8	76
Ewe . . .	4·9	6·5	6·9	109
Mare . . .	5·7	1·3	1·2	29

nutrient for the bacterium *Lactobacillus bifidus* (variant Penn). This nutrient is not found in cow's milk. It is a nitrogen-containing polysaccharide with a high hexosamine content. The biological significance of this substance for the young infant is not known, but it is interesting that the prevailing micro-organism in the fæces of normal breast-fed infants is *Lactobacillus bifidus*. By contrast, the fæces of infants fed on cow's milk contain a great variety of organisms. The fæces of breast-fed infants are acid, whereas the fæces of infants fed on cow's milk are usually alkaline or neutral. Perhaps the intestinal flora favoured by human breast milk aids the efficient utilisation of its protein.

The fat in freshly secreted milk is present in fine globules, many of which are as small as 0·5 μ in diameter. Fat in this form is particularly easily digested. When milk is left to stand these globules run together to form cream. The fat content of human milk varies greatly, as does that of cows.

In some mammals the fat content of the milk is very high. The milk of whales and sea lions, for instance, contains over 40 per cent. of fat. In these animals lactation lasts for a very short period, during which the mothers cannot feed. The milk transfers an enormous quantity of fat from the mother to the young in the course of a few days. Elephant's milk contains 20 per cent. fat and reindeer milk 17 per cent.

The carbohydrate in all milks is lactose. This sugar is much less sweet than cane sugar. Human milk contains more lactose than cow's milk. Cow's milk is frequently ' humanised ' by diluting and then adding cane sugar or glucose. The young infant thus becomes accustomed to an unnaturally sweet food at an early age.

Calcium is present in all milks in good quantities. Human milk usually contains between 25 and 35 mg./100 ml. Cow's milk contains about 120 mg./100 ml. The calcium is present chiefly in combination with caseinogen. For some unknown reason milk also contains significant amounts of citric acid—up to 0·23 mg./100 ml.—which must reduce the ionisation of a small part of the calcium. Nevertheless the calcium in milk is generally more readily absorbed than that in other foods, probably because of its combination with amino acids. Milk is thus a most valuable food for the formation of bone.

Phosphorus is found in human milk in concentrations of 10 to 20 mg./100 ml. Cow's milk may contain 100 mg./100 ml.

Iron.—Milk contains very little iron. All milks provide 0·1 to 0·2 mg./100 ml. Young mammals depend for their initial supply of iron on stores accumulated during intra-uterine life. In the human infant these stores are sufficient for only 4 to 6 months, and if iron is not then provided in the diet anæmia is likely to follow.

Vitamins.—The vitamin content of milk often reflects the vitamin content of the mother's diet. This is most important in the case of thiamine.

THIAMINE.—Infantile beriberi is liable to occur in breast-fed infants when the maternal diet is deficient in this vitamin. The thiamine content of mother's milk in Europe and North America falls within the range of 10 to 20 μg./100 ml. once lactation is fully established, though in the first 14 days of lactation it may be less. Cow's milk contains about 45 μg./100 ml.

Simpson and Chow (1956) in Malaya and Plagnol and Dutrenit (1956) in Viet Nam have shown that the thiamine content of the milk of Eastern women with healthy babies also falls within this range. But the milk of some women whose infants were believed to be suffering from beriberi contained very small amounts of thiamine—0 to 6 μg./100 ml. To raise the thiamine content of the milk of these women to a level safe for the children (15 μg./100 ml.) a supplementary supply of thiamine was necessary.

THE RIBOFLAVIN content of human milk in early lactation is about 20 μg./100 ml. and may rise to 45 μg./100 ml. Cow's milk may contain 200 μg./100 ml. The riboflavin content of milk seems to be very much dependent on the dietary intake of the pregnant woman or animal.

THE NICOTINIC ACID content of milk has been little studied. Walker (1954) found that European women in Johannesburg gave milk with a nicotinic acid content between 110 and 300 μg./100 ml., but Bantu women's milk contained 15 to 140 μg./100 ml. Cow's milk contains about 100 μg./100 ml.

Provided the mother's diet is not grossly deficient, human milk is a satisfactory source of the B group of vitamins, as also is cow's milk which, in small quantities, will usually cure angular stomatitis, glossitis and other conditions associated with riboflavin and nicotinic acid deficiency.

ASCORBIC ACID is usually present in the milk of British mothers in amounts between 2 and 5 mg./100 ml., so that their infants may receive up to 50 mg. daily, which would appear to be more than adequate. Cow's milk contains much less—only about 1 to 2 mg./100 ml. This small amount is easily destroyed by pasteurisation and boiling of milk or allowing it to stand in sunlight. Cow's milk is thus a relatively poor source of ascorbic acid, and infants fed solely on cow's milk must be given a supplementary source of this vitamin.

VITAMIN A.—British mother's milk usually contains 25 to 45 i.u. of vitamin A/g. of fat and in addition a small amount of carotene. Unless the mother's diet is grossly deficient breast-fed infants appear to receive a sufficiency of this vitamin. Keratomalacia is very rare in breast-fed infants. Cow's milk has a vitamin A content which varies from 70 to 150 i.u./100 ml. It is higher when the cows are out in good pastures than when they are stall-fed in winter.

THE VITAMIN D content of human milk has been little studied. Kon and Mawson (1950) report values between 0·13 and 0·41 i.u./g. of milk fat.

THE DIGESTION OF MILK

Milk clots when it enters the stomach. This is due to the action of an enzyme—rennin. The clotting of milk converts the caseinogen into insoluble casein. The casein clot contracts into a tough mass which is subsequently digested. Infants secrete little pepsin in the stomach ; the clot is digested by trypsin and other proteolytic enzymes in the small intestine. The biological significance of this clotting is not known ; it is reputed to make milk less easily digested. It can be partially prevented by diluting the milk with water, thus reducing the concentration of calcium which is necessary for the formation of the clot. Clotting can also be prevented by the addition of sodium citrate. Both these means have been much used, but whether they increase the digestibility of milk is doubtful. Milk is, in fact, readily digested and absorbed, especially by infants and growing children.

Cow's milk—owing to its high protein content and its content of phosphate and citrate—exerts a strong buffering action, thus lowering the acidity of the gastric juice. It is perhaps for this reason that milk is often so effective in reducing the pain caused by a peptic ulcer and the associated hyperacidity.

MILK PRODUCTS

Soured and fermented milks.—In many countries, milk is drunk sour or curdled. Various bacteria are used for this purpose—*Lactobacillus acidophilus* found in man, *L. bifidus* found in the alimentary tract of infants and *L. bulgaricus* found in cows. All these bacteria cause a breakdown of the lactose in the milk with the formation of lactic acid (up to 3 per cent.). The natural method of preparation is to boil the milk and somewhat reduce its volume. After cooling it is inoculated with a small portion of the previous day's milk as a starter. The souring takes about 24 hours. Condensed and reconstituted dried milk can be used for the purpose. Commercial preparations of the bacterial cultures are also available as starters. Sour milk (yoghurt) contains all the protein, fat, calcium and vitamins of the original milk. It is a safe preparation in countries where standards of dairy hygiene are low, for the original milk is sterilised by boiling and the subsequent profuse growth of *L. acidophilus* will overgrow any chance pathogenic contaminant. There are many traditional forms of sour milk which are appreciated as national drinks.

Yoghurt is made in Greece, Romania, Hungary, Bulgaria, Turkey, the Caucasus and neighbouring countries. Cow, goat, sheep or buffalo milk may be used. If the milk has been much concentrated by boiling, the yoghurt is diluted with water for drinking and is then known as *doogh* in Afganistan and Iran, or *eyran* in Turkey. If souring is allowed to take place when the milk is warm (about 55° C.), a preparation known as *laban* is formed, which may contain a little alcohol from yeast fermentation. *Kefir* is a sour milk made in the Caucasus with lactobacilli and a lactose-fermenting yeast, which may have an alcohol content of 1 per cent. *Kowmiss* is a popular Russian drink prepared from mare's milk, which is rich in lactose. It may contain up to 3 per cent. alcohol. Yoghurt, as usually prepared and obtained in Britain and the U.S.A., can, however, be safely consumed by the strictest teetotaller.

The great Russian scientist Metchnikoff at the end of the nineteenth century conceived the idea that yoghurt was an elixir of life. His theory was that the putrefactive bacteria present in the large intestine produce toxins that shorten life. He thought that by taking yoghurt, the milk-souring bacilli would become dominant in the intestine and oust the normal putrefactive bacteria. He himself took yoghurt regularly and established it as a fashion in many European cities. There was not a shred of evidence to support Metchnikoff's theory which is now quite discarded. Yoghurt is a nutritious and pleasant food, but has no unique nutritive properties.

Dahi is a sour milk preparation made in innumerable Indian homes. Whole milk is brought to the boil and then allowed to cool to about body temperature and kept at this heat in an earthen vessel. A small amount of yesterday's dahi is added as a starter. When cool, dahi is a delicious drink, especially in the hot weather, although perhaps an acquired taste for Europeans. The butter fat may be removed from dahi by churning and used to make *ghee*. The remaining sour milk is known as *lassi* and is also a popular drink.

Buttermilk is a term which may be used in Europe for a variety of products. In Holland and Denmark it is prepared when sour cream is churned into butter, and is a popular drink.

Curds are the clotted proteins formed when fresh milk is artificially inoculated with rennet (a commercial preparation of rennin, prepared either from calves' stomachs or vegetable sources).

Whey is the fluid that separates from the clot in making curds. It contains most of the lactose in the original milk, and a little lactalbumin, but almost no casein or fat ; its nutritive value is therefore small. Though once in vogue in a variety of therapeutic regimes, it is now seldom, if ever, prescribed.

Butter is discussed later in this chapter.

Cream contains all the fat and usually from one-third to half of the protein and lactose in milk. From time to time the British Government has laid down standards for the minimum fat content of cream.

The famous *Devonshire cream* or clotted cream is prepared by heating the milk in special pans. This brings about a rapid and effective separation of the fat. Devonshire cream may contain 60 per cent. of fat.

Skimmed milk is milk from which the fat has been removed in the making of butter or cream. It is a by-product of the butter industry and since it is readily dried, large quantities of the dried product are available on the world market. In Great Britain skimmed milk has been traditionally fed to pigs and is despised as a human food. This is unfortunate, since it contains most of the protein and nearly all the calcium in the original milk. It also contains the B group of vitamins. Skimmed milk is thus a very good food. Largely through the good offices of the United Nations International Children's Emergency Fund (UNICEF) many thousands of tons of dried skimmed milk have been distributed to children in countries which are short of dairy cattle. The improvement in health of children receiving this milk has been demonstrated in controlled experiments and vast numbers of children have benefited.

Casein.—Various preparations of casein are on the market. Casilan, a calcium caseinogen, is one which is well known. These preparations have little taste and can be added to soups, puddings, milk drinks, cocoa, etc. They provide a most convenient and effective means of enriching diets with protein in dietetic practice, as for instance in the treatment of burns, prolonged fevers and in convalescence from severe illnesses.

Cheese.—Milk production is inevitably subject to large seasonal variations. In the summer months when pastures are good, cows yield more milk than in the winter ; some summer surplus is therefore common. Cheese-making is an effective method of preserving some of this surplus and has been a traditional occupation of European farmers' wives for generations. Methods vary greatly ; Mottram and Graham state that there are 400 known varieties of cheese.

The basic process in cheese-making is the clotting of the milk. The milk may or may not be soured first. Rennet is used to form the clot, usually at a temperature of about 30° C. The clot, which contains almost all the protein in the milk, also entangles the fat and many of the other nutrients. The clot is then gently separated from the whey and salted. It is pressed to remove moisture and a firm cake is made. The cheese is then put in cheese bags and kept in a cool room to ripen. During ripening bacterial fermentation takes place ; the particular bacteria and moulds responsible give the cheese its characteristic texture and flavour. Many variations in the details of cheese-making exist. Cow's milk is usually employed, but Roquefort cheese comes from ewe's milk and some

Norwegian cheeses from goat's milk. The blue colour in Stilton, Camembert and Roquefort is produced by moulds developing during the ripening process. The most famous English cheeses are Cheddar, Cheshire, Wensleydale and Stilton. France produces the greatest variety: Camembert, Brie, Livarot and Pont l'Eveque are famous French soft cheeses; Roquefort, Saint Paulin and Pont-du-Salut are semi-soft cheeses. Italy produces the blue Gorgonzola, semi-soft Bel Paese and the hard Parmesan. Limburger is a soft, strongly flavoured Belgian cheese. Holland produces many notable Dutch cheeses—particularly the round red Edam—and Denmark the famous Danish blue.

The liking for cheese is curiously variable. In a survey (Kitchin *et al.*, 1949) among Edinburgh University students when cheese was rationed it was found that a third of the students never ate their ration: but others managed to acquire three or even four official rations (60 g. weekly). Similarly, though many coal miners—notably in Wales and in the Midlands—eat large quantities of cheese with their underground meal, Durham miners will not touch it.

Those who will not eat cheese forego a food which is not only tasty but also most nutritious. Most cheeses contain 25 to 35 per cent. of protein and this protein is of very high biological value. The fat content varies from 16 to 40 per cent. Cheeses are also rich in calcium, vitamin A and riboflavin.

In Great Britain during the 1939-45 war, cheese-making passed largely out of the hands of the farmers' wives and into the large factories. Now that farmers are producing a surplus of liquid milk—which they are finding difficult to sell—it is to be hoped that they will persuade their wives to take up again this traditional craft.

Khoa, churkom, dried reindeer milk and other delicacies.—Cheese-making is characteristically a European art. There are, however, a number of ways in which surplus milk can be concentrated, sometimes into forms which may be preserved for a long time. In India, *khoa* or *mawa* is made by boiling milk briskly in an open pan until about two-thirds of the water has been evaporated and it has the consistency of dough; *rabri* is made by skimming off successive layers of cream from simmering milk and adding sugar when the liquid residue is greatly reduced; the skimmed-off clots are then blended back into the residue to make a sweet concentrate. In the Himalayas the Sherpas heat any excess lassi and the clot formed, mainly casein, is strained through bamboo baskets and then dried before an open fire to make *churkom*. In Lapland reindeer milk is put in a reindeer stomach over an open smoking fire. As the water evaporates and the milk is 'cured,' more is added and it may take two or three weeks before the stomach is filled with grains of the dried milk. The contents of a full reindeer's stomach may last a Lapp family for the winter.

Nearly all indigenous milk products have the advantage that they are much less likely to be contaminated with pathogenic organisms than fresh milk. They can therefore be strongly recommended in places where the standards of dairy hygiene are low. Further information about the diverse milk products in the world can be obtained from a report by a committee of the Food and Agriculture Organisation and the World Health Organisation (1960).

2. OILS AND FATS

These are valuable foods because (1) they have a high caloric value and thus are a concentrated source of energy ; (2) they are essential to the art of good cooking, as practised in all civilised countries ; (3) some oils and fats are important sources of fat-soluble vitamins. As already discussed in Chapter 6, good cooking demands that at least 20 per cent. of the calories in the food should come from fat. This applies to traditional methods of cooking both in the West and East. Fats and oils are expensive, so that this level is often not achieved by poor families. Amongst the well-to-do, fats and oils often provide 40 per cent. of the calories ; there is clear evidence that—in sedentary people at least—such a high intake disturbs the normal mechanisms for the transport of fat in the blood ; this may lead in turn to fatty degenerative changes in the arteries and an increased tendency to thrombosis, as described in Chapter 40.

Butter (milk fat) is generally the housewife's favourite : but the depot fat from the carcasses of many animals is also used for cooking. Vegetable oils used for cooking in many parts of the world include olive oil, cotton-seed oil, coconut oil, red-palm oil, soya-bean oil, groundnut oil, mustard oil, gingelly (sesame) oil and linseed oil. In the last 50 years there has been an enormous increase in the manufacture of hardened fats—artificial butters—out of vegetable and marine oils. Margarine manufacture is now a major industry.

The principal constituents of all fats and oils are the triglycerides or neutral fats. Fats contain very little water ; the caloric value of all food fats and oils is very high and lies between 800 and 900 Cal./100 g. As described in Chapter 6 the natural fats vary greatly in the nature of the fatty acids which they contain. These variations do not affect the caloric value of the fat or oil ; but they do determine the consistency of the fat. A high proportion of saturated fatty acids—as is present in land animals—gives a fat which is hard or solid at room temperature. A high proportion of unsaturated fatty acids—as is present in marine animals and vegetable seeds—gives an oil, liquid at room temperature. The ratio of polyunsaturated fatty acids to saturated fatty acids may be an important factor in the pathogenesis of atherosclerosis (Chapter 40).

MARGARINE AND BUTTER

A French chemist Mège-Mouries made the first recognisable substitute for butter in 1870, stimulated by the shortage of the natural product during the Franco-Prussian War. He used suet (beef or sheep fat). At about the same time there was a growing need for a cheap substitute for butter for the industrial populations in the big towns of Western Europe and the U.S.A. At first animal fats were used; the recently developed meat-packing industry in Chicago rapidly produced these fats as a by-product. But supplies were soon insufficient. At the end of the nineteenth century—largely as a result of Dutch enterprise—ways were found of hardening vegetable oils by hydrogenation.

The vitamin content of butter depends on the quality of the cows' diet. Good summer butter may contain up to 4000 i.u. of vitamin A/100 g., but winter butter as little as 1500 i.u. The vitamin D content of butter varies from 10 to 100 i.u./100 g. In Great Britain vitamins are artificially added to margarine: 2500 to 3200 i.u. of vitamin A/100 g. and 270 to 340 i.u. of vitamin D/100 g., *i.e.*, as much vitamin A and more vitamin D than is contained in good butter.

There is no evidence that butter fat as such has any nutritional advantage over margarine, now that margarine is enriched with vitamin A and D. This statement is based on much sound biological work. Groups of rats have been brought up under identical conditions except that one group received all its dietary fat in the form of butter, the other in the form of fortified margarine. Several generations of these animals were observed. No difference between the two groups could be detected, either in respect of the rate of growth of the young, reproductive efficiency of the mothers, length of life or freedom from disease. It has been shown beyond all reasonable doubt that butter and margarine can be freely interchanged in the diet of rats. It is clearly impossible to carry out experiments on this scale in man. However, 276 children in American orphanages were divided into two groups: over a period of 2 years one group received all its table fat as enriched margarine and the other as butter. This experiment failed to demonstrate any difference of growth or of health between the two groups during this period (Leichenger *et al.*, 1948). It seems likely that the great increase in health of the children of Great Britain that took place between 1920 and 1945 can be attributed in part to their increased consumption of *enriched* margarine.

GHEE

In India and in other parts of the East, butter fats are first clarified by heating and the resulting product is known as *ghee*. Ghee may be made either in the home or as an industrial product. Processes vary. Good ghee may contain almost all the vitamins present in the original milk fat, but losses may be up to 50 per cent.

SUET, LARD AND DRIPPING

In Western countries various cooking fats besides butter and margarine are used. These include suet, lard (pig fat), beef dripping and several commercial preparations. All of these are of high caloric value (800 to 900 Cal./100 g.); the natural ones contain only traces of vitamins.

VEGETABLE OILS

The large number of vegetable oils used in the tropics and Mediterranean countries are all of high caloric value (about 900 Cal./100 g.). With one exception all are devoid of any vitamin activity. It is this fact that makes so many tropical diets low in vitamin A activity. The one exception is red palm oil (from the palm, *Elæis guineensis*), which contains 40,000 to 80,000 i.u./100 g. as carotene. The palm is a native of West Africa where it grows wild and also is extensively cultivated. There are small plantations in India, Malaya and other parts of Asia. In comparative studies in Nigeria, Nicol (1952) has shown that children receiving red palm oil were in better health than those that had none. There is no doubt that in those tropical areas where intakes of vitamin A and carotene are at present low, the introduction of this oil palm would be of immense benefit to health. In many districts in the tropics there appear to be no agricultural difficulties that would prevent the establishment of such plantations. The use of vegetable oils, particularly corn oil and sunflower seed oil, for lowering the level of plasma cholesterol in the hope of reducing the liability to atherosclerosis is discussed in Chapter 40.

SYNTHETIC FATS

It is now possible to synthesise from non-biological material fats which can be used as a human food. Interest in this subject was greatly stimulated in Germany by the war-time shortages of fat. Fats have certainly been prepared synthetically on an industrial scale and many experiments have been carried out to test their nutritional value both for animals and man. A useful review (Food and Agriculture Organisation, 1949) records the different conclusions reached by different observers; unfortunately the tests have sometimes been coloured by political considerations. However, it is an intriguing fact that chemists, as well as farmers, can produce substances which may serve as a source of calories for man. More may be heard of this in the future.

Chapter 21

BEVERAGES—HERBS AND SPICES—MISCELLANEOUS—NEW AND IMPROVED FOODS

BEVERAGES

THE needs of the human body for water have already been discussed in Chapter 10. To meet them man must drink. All experience shows that *homo sapiens* is not very fond of plain water. He usually prefers to drink flavoured fluids such as beer, wine, spirits, tea, coffee, cocoa, fruit juice, or even synthetic ' colas ' and ' lemonades.' Modern man can choose from a great variety of beverages and, as far as the purse allows, he chooses one of them in preference to plain water.

Beverages are appreciated for their flavour and for the pharmacological action of the drugs that many contain. Some are also a source of calories and a few provide significant amounts of minerals and vitamins. Before describing the principal beverages, it is proper to consider these points briefly.

Flavour

This is provided by the essential oils in the herbs, berries, and other fruit and grains which go to form the basic ingredients of many drinks. In tea and coffee gardens, in orchards, hop fields and vineyards, cultivators use the experience of generations to produce the best raw materials. Tea blenders, vintners, distillers, housewives and many others use traditional skills to refine and concentrate the basic ingredients. All humanity is grateful for the labours of such skilled craftsmen. To the epicure with a trained palate, the appreciation of well-made tea and coffee—of fine wines and spirits—is one of the privileges of living in a civilised society. Chemists are now moving into this field of knowledge, but they are not yet as reliable as wine tasters, tea tasters and other experts with long-standing traditions. The chemistry of ' Bouquet and Essence ' is discussed in a learned editorial in the *Lancet* (1961*a*) with references to appropriate French and German literature. The supreme qualities of ' Scotch ' still remain a mystery, immune from science.

Drugs

Caffeine, theophylline and theobromine are present in small amounts in tea, coffee and cocoa. They are methyl derivatives of xanthine. Caffeine is the most active ; it is a stimulant to the nervous system and often prevents fatigue ; many people find that caffeine appears to facilitate mental work. Most people in western countries are habituated to caffeine ;

they are accustomed to take it, but they do not become addicted to it. The British housewife, who is so frequently 'dying for a cup of tea,' may feel tired and frustrated if she does not get it, but otherwise suffers no serious symptoms.

An excessive intake of caffeine can cause sleeplessness and so may aggravate emotional instability and mental illness. In some persons it appears to augment the sensitivity of the heart to emotional and toxic factors and so increases the incidence of extrasystoles and other arrhythmias ; otherwise it is doubtful if any ill effects arise from the use of tea and coffee. Both contain tannin which is a weak protein precipitant and astringent. Much has been written about the effects of tea and coffee on digestion and the alimentary canal ; they are often prohibited for patients with gastritis and peptic ulcer. There is little scientific evidence to justify this. Certainly tea and coffee do not impair digestion when taken in moderate amounts and not excessively strong, whether by healthy people or patients. If a patient complains that they seem to cause indigestion it is clearly wise to advise curtailment, but complete prohibition should rarely be necessary.

Caffeine is a weak diuretic. It is of little medicinal value for this purpose, nor are tea and coffee contraindicated for this reason.

Alcohol.—This drug depresses the higher nerve centres. Its first effect is to reduce the sense of worry and so to promote a feeling of well-being. It also loosens the imagination. Men and women come out of themselves, are more sociable and generally less intolerant of their fellow beings. For these reasons alcohol promotes good fellowship. If not abused, it is a valuable social drug which has been appreciated by many civilised men.

Alcohol, even in small doses, impairs the judgment and inhibits the skills necessary for fine movements. Euphoria usually prevents the subject from appreciating this loss. It is in this way that alcohol is so specially dangerous for motorists, even in small amounts.

Large quantities of alcohol lead to drunkenness, and if taken regularly addiction follows. The chronic alcoholic is one of the most pitiable problems of medicine.

For these reasons many thoughtful people are total abstainers and advocate total abstinence for others. Of the four men who have had the greatest influence on human thought, two—Jesus Christ and Socrates—are reputed to have been wine-drinkers. The other two, Gautama Buddha and Mohammed, are said to have been abstainers. Lesser men are similarly divided, though the divisions do not always follow religious lines. Whatever one's personal views, it is important to appreciate the sincere opinions of others. We ourselves believe that alcohol has a valuable role in promoting social intercourse and thereby health. In certain circumstances alcohol is a valuable drug in the treatment of disease ; it can stimulate appetite, act as a useful bedtime sedative—especially for elderly or injured people—and is a good source of calories.

NATURAL WATERS

The most important quality of a natural water is that it should be free from pathogenic organisms. Typhoid fever, cholera, amœbic and bacillary dysentery are the most important waterborne diseases. The constant vigilance of water engineers and public health authorities is necessary to protect civilised communities from these diseases. So accustomed have many of us become to the services of these experts that they are often too readily taken for granted. In countries where clean water is not available everywhere, much ill-health is attributable to water-borne diseases.

Natural waters may contain too little iodine and too little or too much fluorine. The effects of these have been discussed in Chapter 12. Soft waters contain little or no calcium, but very hard waters may contain 200 mg. calcium/*l.* or more and so may provide a useful proportion of the daily intake of this mineral. Such very hard water has been reputed to cause dyspepsia in some susceptible persons, but on no very good evidence.

MINERAL WATERS

Natural springs of water with a strong odour or taste have always excited the imagination of man. From time immemorial healing powers have been attributed to such mineral waters ; and indeed in more credulous times many were accredited with miraculous properties. All over the world there are watering-places and spas whither many resort to drink the waters in search of health. There is, of course, no doubt that large numbers of patients have benefited from visits to spas. Such benefit however can usually be attributed to a change of regimen and a new and more regular habit of life rather than to any special medicinal property of the water. Indeed the mineral salts present in many spa waters are in such low concentrations as to be virtually devoid of physiological or pharmacological action.

Mineral waters contain small quantities of sodium chloride, sodium carbonate and bicarbonate, also salts of calcium and magnesium and sometimes iron or hydrogen sulphide. They are usually mildly alkaline. The total mineral content is seldom as high as 8 g./*l.* and is often much less. Many of these waters are naturally aerated with carbon dioxide.

The best-known waters come from France and Germany. Perrier, Contrexéville, Vichy, Apollinaris and Evian waters are bottled on a large scale and have a world-wide sale. Their pleasant sharp taste makes them refreshing to drink and for this they can be recommended. Inasmuch as their use may restrict the intake of other less desirable beverages, they may promote health.

The popular modern taste for carbonated water as a diluent or ' mix ' for alcoholic drinks or fruit juices no doubt derives from the earlier taste for naturally aerated waters. ' Soda water ' in its familiar siphon is simply water from any wholesome source, with carbon dioxide forced into it under pressure. It has no medicinal properties.

SOFT DRINKS

1. **Fruit drinks.**—An immense variety of lemonades, squashes and fruit juices are sold. Fresh home-made drinks and some high-grade commercial preparations may be good sources of ascorbic acid. In others, however, the vitamin may have been largely destroyed in the processing. It is therefore not safe to rely on a commercial preparation of fruit juice as a source of ascorbic acid without analysis. Such juices have a variable caloric value dependent almost entirely on their sugar content. Many fruit juices are rich in potassium and relatively poor in sodium. They are thus useful for patients with cardiac œdema and others for whom a low sodium diet has been prescribed since they provide a pleasing variety to an otherwise dull diet.

Fruit juice has become an almost essential component of the American breakfast. This is a pleasant habit, which might well be exported to more European homes.

2. **Synthetic soft drinks.**—The label ' lemonade ' is often used for products that have never seen a lemon. Indeed there are many synthetic ' ——ades ' and ' colas ' which often contain little more than sucrose or glucose, some citric acid or tartaric acid and colouring or flavouring agents. For appearance or flavour a certain minimal amount of fruit pulp may be added. The exact composition of many of these drinks is a secret of the manufacturers. The suspicion exists that their cost to the consumer is often out of all proportion to the cost of their basic ingredients. Because of their variable sugar content they are contraindicated for diabetics and obese patients. In at least one instance the content of glucose is advertised as especially valuable for giving energy ; in fact, however, glucose taken by mouth is in no way superior to sucrose as a source of calories.

These drinks contain little or no vitamins or minerals. In general they are scarcely more than an agreeable but often expensive way of taking fluids.

TEA

Tea has been drunk in China for thousands of years. It was introduced into Europe in the seventeenth century and was at first a great luxury. After the discovery that tea could be grown easily on large estates in Ceylon and India, enormous quantities were imported into Great Britain, where for nearly a hundred years it has been a cheap and popular beverage.

Several varieties of the shrub are cultivated. Fertile soil, a warm climate and a good rainfall are necessary conditions for growth and these are found in Ceylon, Assam and the hill districts of South India. The shrubs are allowed to grow up to a height of about 4 ft. and are pruned each year. The young and tender leaves, ' two leaves and a bud ' of each shoot, are picked by hand, usually by women. After picking, the leaves are taken to a factory, usually on the estate, where they are withered, mashed or rolled and allowed to ferment. They are then dried. Most Indian and Ceylon tea sold in Great Britain is blended by mixing samples grown on different gardens.

Green teas commonly consumed by the Chinese are withered at high temperatures, so that the enzymes responsible for the fermentation are destroyed and this process in the manufacture is omitted.

The great variety of teas on the market are of interest to the connoisseur, but not to the physician or dietitian. They can be recommended as an attractive drink to all except a few unfortunates, in whom tea appears to cause indigestion, probably owing to the tannin present. Mottram and Graham (1956) report the analyses of many types of tea ; they found the tannin content of a cup (150 ml.) of infusion to vary from 80 to 280 mg. Caffeine contents varied from 50 to 90 mg. The mild stimulating effect of caffeine has already been described. The pharmacopœial dose is 60 to 300 mg., so that many cups have to be drunk before this is exceeded.

The usual British custom (though not practised by connoisseurs) is to add sugar and milk. In this way some people may obtain a significant addition to their intake of calories and protein.

COFFEE

Coffee beans are the seeds of coffee trees that are widely cultivated in the tropics. They have been grown in Abyssinia and Arabia for hundreds of generations. There are large plantations in India, Ceylon, Indonesia and especially in Brazil.

A variety of trees are grown. Most coffee trees are small—10 to 15 ft. high—with evergreen leaves. Shade trees are necessary to protect them from excessive sun. They bear clusters of white flowers which develop into the beans. A tree provides the best crop when between 6 and 14 years old ; it requires regular and skilful pruning.

The beans have to be roasted and ground before the infusion is made. Sir Robert Hutchison found about 100 mg. of caffeine and 200 mg. of tannin in a teacupful of coffee, made by infusing 2 oz. (60 g.) in a pint (450 ml.) of water (Mottram and Graham, 1956). Coffee thus normally contains about as much caffeine and tannin as tea.

Coffee rapidly loses some of its flavour after grinding ; the best coffee is made from beans ground in the home. Various preparations of dried ground coffee are on the market. These are convenient, but of inferior quality to freshly ground beans. There are many ways, each with their own champions, of making the infusion.

Coffee is frequently adulterated and—especially in times of scarcity—a great variety of substances are used for this purpose. The most important is chicory which is especially common in French coffee. Chicory is the root of a wild endive. It is dried, partly caramelised and then added to coffee in proportions varying from 10 to 80 per cent. Chicory's great attraction is its cheapness. There is no reason to think that it is in any way injurious to health.

Cocoa

Cocoa is made from the fruit of a tree indigenous in Central and South America. It is a small tree—about 20 ft. high—and grows only in damp tropical lands. Cultivation has spread from tropical America to West Africa, Ceylon and other parts of Asia. West Africa now provides the greater part of the world's supplies. The fruit is a gourd in which the numerous seeds are embedded. The seeds are removed from the pulp, placed in heaps and allowed to dry in the sun for several days. During this process they lose their bitterness and acquire the pleasant taste characteristic of cocoa. The seeds are then roasted and ground.

The chief xanthine derivative in cocoa is theobromine, but it also contains some caffeine and tannin.

Comment

Coffee, tea and cocoa are so much a feature of British everyday life that it is hard to realise it is less than 400 years since they were introduced into Europe, and less than 100 years since the development of large well-organised plantations and gardens in the tropics enabled them to be produced sufficiently cheaply to become available in even the poorest homes. Essentially they are luxuries, for they are refined products dependent on the skill and industry of innumerable craftsmen. Yet they are produced at a price within the reach of all but the poorest. As with all other fine products, some skill and care is needed for their proper use and appreciation. Nowadays this is too often lacking. There is almost no medical contraindication to their use. Judiciously consumed they can do much to break the monotony of restricted therapeutic diets.

In the social sphere tea, coffee and cocoa have been invaluable, since they provide an alternative means of hospitality to alcoholic beverages. As such they have proved useful in preventing the abuse of alcohol.

Alcoholic Drinks

From the earliest times man has used yeasts to ferment carbohydrates and so to produce ethyl alcohol (ethanol). In contrast to many other products made by the action of micro-organisms on foodstuffs, ethanol is easily metabolised and has no long-term harmful effects if taken in moderation.

A great variety of carbohydrate sources have been used. The best alcoholic drinks are made from fruit or cereal grains. But there are many other sources, ranging from the sap of palm trees used in Africa to the fermented milk of mares of the Tartars.

Ethanol is seldom the only product of fermentation when micro-organisms grow in a carbohydrate medium; given a good supply of oxygen they generally yield acetic acid instead, with the production of vinegar. The cellulose contained in wood pulp when fermented yields a high proportion of methyl alcohol which—in contrast to ethanol—is highly toxic for man and can cause permanent blindness. Many fermented liquors contain small amounts of higher alcohols (fusel oils) which have toxic effects; they are probably responsible for the 'hangover.' By their traditional art, the brewer, vintner and distiller—aiming at a benign and beneficent drink—generally manage to exclude these toxic products.

Beer, ale and stout

The best brews are made from malted barley. The barley grains are moistened and allowed to sprout for a few days in a warm atmosphere. This activates the enzyme diastase which begins to split the starch in the grains. At the proper moment the activity of the enzyme is stopped by heating ('malting') the sprouting grain in kilns. The temperature at which the malting is carried out determines the final appearance of the brew. For dark beers and stout (also known as 'porter' in London), the heat is sufficiently intense to produce some caramel which gives the colour. The dried malt is ground and then mixed with water to produce the 'mash.' The quality of the water is most important; the waters of Edinburgh, Dublin and Burton-on-Trent have each been the foundation on which large brewing industries have been built. Burton water contains unusual amounts of calcium sulphate. The fluid strained off from the mash is called 'wort.' The wort is boiled with the result that all further enzymic action is stopped and intruding micro-organisms are killed. Generally hops are added during the boiling. Hops not only impart a distinctive bitter flavour to the brew but also the terpenes present in them are thought to have antibiotic properties—against chance contaminants. The wort, once cooled, is piped off into vats where it is inoculated with a pure culture of yeast. The maintenance of a good yeast culture is one of the most carefully guarded and unpredictable secrets of good brewing. A culture of Burton yeast for instance, imported into the U.S.A., produced good Burton beer for a few brews and then, unaccountably (but apparently through mutation) suddenly changed its behaviour and began producing standard American beer instead. In the making of 'light' ales and lager most of the yeast lies at the bottom of the vat so that the wort is charged with the carbon dioxide it produces. When the fermentation has reached the proper stage the wort is filtered off into casks where some further fermentation may take place. Various clearing agents are usually added, such as gelatin, isinglass or tannin—sometimes with additional hops.

In all of these processes the knowledge and skill of properly trained brewers are essential to produce a uniform and reliable product.

Most beers, ale and stout contain from 3 to 7 per cent. of ethanol, though some ‘ special brews ’ may contain much more. Their caloric value is usually between 30 and 60 Cal./100 ml.—about the same as milk. But they differ from milk in that they contain no protein, fat or useful amounts of calcium. The only vitamins present in beer in significant amounts are nicotinic acid and riboflavin.

Country beers and toddies

In many parts of the world country beers are made by fermenting cereals such as maize, millets or rice. Where palm trees grow, toddy can be made by fermenting the sweet sap. Wild yeasts are generally used for the fermentations. Such beers and toddies are usually produced for their intoxicating effects. Their alcohol content varies greatly, and may be as little as 1 per cent. or as much as 7 per cent. This alcohol is, of course, a source of calories, and country beers and toddies may also contain thiamine, riboflavin, nicotinic acid and ascorbic acid in amounts which are nutritionally significant. Thus these beverages are sometimes useful foods. Platt (1955) has given an interesting account of the alcoholic drinks traditional amongst indigenous Africans. In some villages, excessive amounts are drunk and this may be responsible for much poverty and ill-health. Elsewhere, the beer may be a valuable supplementary food and a useful ‘ cement ’ to the cultural life of the village. In Africa, as elsewhere, alcoholism is an old problem, but reformers should not condemn these country beers and toddies hastily, without a knowledge of the social circumstances and the amounts of alcohol and vitamins usually derived from them by the local people.

Mead, cider, country ‘ wines ’

As Platt (1955) pointed out, mead made from honey was perhaps the first alcoholic drink. Certainly Homer and the writers of the Norse sagas were familiar with it. The Roman conquerors of Great Britain tried hard to introduce wine in its place ; relics of their efforts remain in the terraced hillsides overlooking the Severn river. Wine-making continued on a small scale in the mediæval monasteries in order to provide for the Eucharist. But in our cold and uncongenial climate, the only fruit that could be depended on to produce fermentable sugars was the apple. Cider made from fermented apple juice was the *vin ordinaire* of the British.

A few people in Great Britain still make their own home brews, such as cowslip, elder and dandelion ‘ wine.’ The wild yeasts present in these materials, mixed with raisins or some other good source of sugar, generally produce a benign and sometimes potent brew.

Wines

The grape is unique among fruits in that no additional sugars need be added to enable wild yeasts present on the fruit to carry out a satisfactory fermentation. In the making of wine the French are pre-eminent ; the great clarets, sauternes, burgundies and champagnes—Château Lafite, Château d'Yquem, Richebourg, Veuve Clicquot—are names to conjure with. Then there are the German wines of the Rhine and Moselle—the Schloss Johannisberg and Berncastler Doktor. All these are the proper delight and solace of civilised Europeans. Other countries also produce some fine wines and every gourmet has his favourite. Italian, Greek, Iranian, South African, Australian, Chilean and Californian wines all have their special virtues. Taken with a meal they are excellent adjuvants to appetite.

But there is also a dark side to the story of wine. In the grape-growing areas of the world *vin ordinaire* is the common drink of the people. If wine is used to quench thirst in a hot climate it is liable to produce cirrhosis of the liver. Natural wines contain 8 to 13 per cent. of ethanol and some unfermented sugars, but no other nutrients in significant amounts. One bottle (650 ml.) of *vin ordinaire* provides about 450 Cal.

Fortified wines, such as port and sherry, have alcohol added to raise the concentration to about 20 per cent. by volume.

An admirable account of the making of wines and of their individual qualities has been provided by Marrison (1957).

Spirits

The art of concentrating ethanol by distillation from fermented liquors was probably discovered by one of the great Arabian physicians despite their traditional abstinence. The word 'alcohol' is derived from the Arabic—*al Kohl* (the powder). Most likely it was first prescribed solely as a drug.

The number and variety of distilled spirits used by modern man is legion. Only the most notable can be mentioned here.

Whisky.—The name derives from the Gaelic *uisgebeatha* (water of life) and certainly much of life in the Scottish Highlands still revolves round it. In a similar way the French call brandy *eau-de-vie*, the Italians *acquavite*, whilst the Danes call their spirits *akvavit.*

Most Scotch whisky now on sale is 'blended' from a mixture of pot-stilled 'malt' whisky with 'patent-still' grain spirit. The unique flavour and aroma of pure malt whisky is probably due to the fact that the wort from which it is distilled is made from barley, malted over peat fires. The method of distillation in pot-stills—based on the principle of the alchemists' retort—also adds something to its quality. Potentially toxic substances present in the first distillate and those remaining in the pot are discarded. Pure malt whisky is the best way to 'treat' a Highlander.

Patent 'Coffey-still' whisky is produced by spraying wort into a tall wooden chamber into which superheated steam is introduced from below. The various alcohol-containing fractions are drawn off by pipes placed at different levels in the chamber. The alcohol so produced forms the body of most exported 'Scotch.'

The best Scotch is matured for at least seven years in oak casks which have previously contained sherry. From them it acquires the characteristic colour and loses its initial rawness by esterification of its higher alcohols.

The strength of a whisky is generally stated in terms of ' proof.' ' Proof ' spirit is traditionally of such a strength that gunpowder will ignite when mixed with it in a teaspoon. Nowadays the meaning ' proof ' is more precisely defined. At 51° F. proof spirit contains 57·07 per cent. alcohol by volume or 48·24 per cent. by weight. Whisky sold in Great Britain is almost uniformly 70 per cent. proof, *i.e.* the alcoholic strength is approximately 30 per cent. A standard bottle of whisky containing 700 ml. therefore provides about 230 g. of ethanol, which at 7·1 Cal./g., amounts to 1600 Cal. But apart from its caloric value, whisky has no other purely nutritional virtues.

For more information about the manufacture and virtues of Scotch whisky, the reader is referred to two good accounts (Robb, 1951 ; Bruce-Lockhart, 1960).

Other whiskies

Irish.—Irish whiskey has much the same qualities as Scotch, though most is kept for home consumption and little is exported. ' Poteen ' is the traditional name for the product of the illicit stills, at one time commonly hidden in the hills.

Bourbon.—This is ' the water of life ' for gentlemen of Scottish ancestry living in the Southern States of the U.S.A. The mash consists chiefly of maize (' corn ') to which some malted barley or wheat is added. Originally it was matured in casks that had been used to import molasses. Nowadays the casks are deliberately burnt on the inside to reproduce the traditional flavour.

Rye whisky is made in Canada and the U.S.A. The best brands are produced with the same care and technique that go to make Scotch.

Other distilled spirits

Brandy.—' Une fine champagne '—a brandy distilled from champagne grapes—is the perfect ending to a gourmet's meal. No other distilled spirit has such a fine aroma or is prepared with so much care. The names of Cognac and Armagnac are justly celebrated by *bon-viveurs* throughout the world.

Rum.—Molasses provide the carbohydrate from which this distilled spirit is prepared. It was the crude drink of those who had traffic among the sugar-cane growing islands of the West Indies, such as British sailors and New England slavers. Nowadays some well-matured and gentle rums are produced.

Gin.—This is essentially a Dutch drink. It arrived in Great Britain when William of Orange succeeded to the British throne at the end of the seventeenth century. Properly made, it is an almost pure aqueous solution of ethanol, derived from a variety of sources, but deliberately flavoured by the addition of various vegetable agents, of which juniper (*genièvre* in French—hence ' Geneva ') is the principal ingredient. Gin thus differs from the spirits so far mentioned in that its flavour is due to additives rather than the materials from which it is made. Unfortunately in eighteenth-century Britain almost any crude distilled spirit was cheaply and freely sold as ' gin ' with tragic consequences to the desperate inhabitants of the verminous city slums. Nowadays gin is a civilised drink and the heart of a good cocktail.

Vodka is another neutral spirit distilled from fermented rye or potatoes. It is the standard liquor of the Russians, but has lately been adopted in the West. It may yet help to smooth out differences of opinion.

Calvados.—This is the traditional liquor of the Celts who live in the westermost parts of France. It is made by distilling cider which in turn is made from apples. A similar liquor is called ' applejack ' in the U.S.A. Vermont farmers make it for their own use, not by distillation, but by leaving the cider barrels outside in the depth of winter. The unnecessary water in the barrels turns to ice, but the ethanol-containing fraction—having a lower freezing point—can be siphoned off into smaller barrels. This process is repeated at each major frost. Thus a hard winter produces real ' hard ' liquor.

Slibovitz is a distinctive drink made in Yugoslavia by distilling fermented plums.

Ouzo in Greece may be any kind of spirit with added flavourings.

Arak.—Once out of Europe or North America the names of distilled liquors and their origins become confused. The word *arak* or *raki* applies throughout most of the East to any distilled spirit. It is usually made by distilling ' toddies ' produced from fermented palm sap and can be very toxic.

Liqueurs.—For centuries monks and other skilled people have worked to produce the perfect ending to a good meal. The best French brandy has obvious pride of place, but after it follow the great liqueurs, made by adding sugar to ethanol, with secret and subtle flavouring agents.

Table 21, 1 gives the alcohol content and calorie value of alcoholic beverages commonly taken in Britain to-day.

HERBS AND SPICES

In all parts of the world civilised man uses these to flavour his food and so make it more attractive and appetising. Large numbers of plants have been cultivated for this purpose. In Great Britain in the Middle Ages, mint, balm and basil, sage and thyme, chives, garlic and fennel, marjoram, horse radish, parsley and many others were grown. There has been a marked loss of interest in herb gardens ; nevertheless there are few gardens in which three or four herbs are not cultivated. In tropical countries, chillies, turmeric, coriander seeds, cumin, cinnamon, cloves, pepper, capsicum and ginger are commonly used. From time

TABLE 21, 1. *Alcohol content and caloric value of common alcoholic beverages* (*McCance and Widdowson*, 1960)

	Alcohol g./100 ml.	Calories per 100 ml.
Beers—		
Brown ale, bottled	2·2	28
Draught ale, mild	3·1	31
Draught ale, bitter	2·6	25
Stout, bottled	2·9	37
Strong ale	6·6	73
Ciders—		
Cider, dry	3·8	37
Cider, sweet	3·7	42
Cider, vintage	10·5	100
Wines, heavy—		
Port	16·1	160
Sherry, dry	15·7	114
Sherry, sweet	15·6	135
Wines, table—		
Champagne	9·9	74
Graves	8·8	73
Australian Burgundy	10·1	72
Beaujolais	9·4	68
Chianti	9·1	65
Spirits (70 per cent. proof)—		
Brandy, gin, rum, whisky	31·5	222

immemorial there has been a profitable trade in spices between the East and Europe.

It is significant that in any part of the world, even in the poorest homes, it is unusual to find neither condiments nor spices. They are essential to the culinary art and promote appetite, good feeding and thus health. Nevertheless they have little direct nutritional value. Individual daily intakes in India may vary from $\frac{1}{4}$ to 1 oz. (7 to 30 g.). The caloric value and protein content of this is negligible. Some condiments such as green chillies are rich in ascorbic acid (100 mg./100 g.); in poor families they may contribute significantly to the ascorbic acid content of the diet. Most herbs and spices contain the B group of vitamins and minerals such as calcium and iron in appreciable concentrations, but the quantities consumed are not sufficiently large to make them significant sources of these nutrients.

Many herbs contain substances which are poisonous to man. Most of these are well known locally and tradition assures that they are avoided. Nevertheless it is possible that herbs containing poisons giving rise to chronic illnesses may still be consumed in some parts of the world. For instance the view is widely held in Jamaica that certain liver diseases may arise from drinking herbal teas (Chapter 39).

In industrial countries natural flavouring agents are being replaced to a considerable extent by artificial chemical ones. A variety of artificial sauces is a feature of the table in most cheap restaurants and indeed in many homes in Great Britain.

MISCELLANEOUS FOODS

Most published tables of food values give a list of about three hundred different foodstuffs. These are the foods on which the vast majority of mankind depend to provide almost all essential needs for calories and nutrients. Yet the number and variety of different foods used by man must run into thousands. Man is in truth an omnivorous animal. The only potential foods that he cannot digest are cellulose and the bones and ligaments of the larger mammals.

Some reference has already been made to the use as food of insects (p. 307), marine invertebrates (p. 309) and fungi (p. 299). Odd and exotic foods add variety and pleasure to the necessity of eating. For the gourmet, caviare and oysters, *écrevisses* and *escargots*, and woodcock stuffed with truffles are *bonnes bouches* which add a rare pleasure to the art of civilised living. But they are not eaten for their biochemical virtues. Among malnourished people on the other hand, living on the fringe of nutritional survival, the occasional titbit of some uncommon food may make all the difference ; for the Bantu child for instance, raised on little else but maize, grasshoppers (when in season) may supply some much needed amino acids. The small boy raised on taro on a Pacific atoll may improve his calcium intake by catching and eating—whole and on the spot—the small fish that abound in the pools of the coral reef. Similarly the West African, dependent for survival on cassava, will derive nutritional benefit from catching and eating a monkey. Nutritionists carrying out dietary surveys in underdeveloped countries must always take note of such adventitious sources of nutrients.

NEW SOURCES OF FOOD

Man is always on the lookout for something new to eat, especially in times of scarcity. New scientific techniques have enlarged the list of possible human foods. An imaginative account of some of these has been given by Pirie (1961). Some proposals are as follows :

1. **Plankton.**—The surface waters of the sea are inhabited by enormous numbers of minute, almost microscopic animals—mainly crustacea and cœlenterates. The potential plankton harvest may be judged from the fact that plankton is the sole food for several species of whale. But the technical difficulties of gathering this harvest are formidable. Plankton when cooked forms a thin sort of gruel with a not unpleasant shrimp-like taste.

2. **Chlorella.**—This unicellular green alga forms the scum on the top of many ponds. Like all green plants, it grows by using the energy of the sun's rays for photosynthesis and can make carbohydrate and protein out of the simple elements of carbon dioxide, water and inorganic nitrogen. The suggestion is that essential nutrients could be extracted from chlorella grown under scientifically controlled conditions, perhaps using atomic energy to promote the photosynthesis. ' Food factories ' operating on this principle would make man less dependent for his nutritional needs on the vagaries of climate—and farmers. Duckweed has also been proposed as an alternative species for this process. The chief difficulty, as with many other new potential sources of nutrients, is how to turn the product into something that people will eat.

3. **Green leaves** are probably the most efficient means of making use of sunlight in order to produce the maximum amount of organic matter on a given area of arable land. Fresh young grass contains good amounts of protein. The traditional way of harvesting this protein is to employ a cow to eat the grass and turn it into milk. But the cow is not an efficient machine in this respect. At least three-quarters of the protein originally present in the grass is lost for human use. Pirie (1956) has devised a process on a small factory scale for extracting protein from leaves without the aid of the cow. His product has the consistency of rather friable cheese and is almost tasteless. It is now undergoing trial as an additive to foodstuffs poor in protein. One practical difficulty is that it cannot be added to all foods because of its green colour : but it will mix well with stews and soups. As yet it has not been developed on a large scale, probably because other more conventional sources of protein are available.

4. **Yeast.**—This is another potentially useful source of protein and other nutrients.

Yeasts are extensively used by man for fermentation processes and for bread-making. Dried yeasts are good sources of the B group of vitamins and of protein. Dried brewers' yeast (*Saccharomyces cervisiæ*) has an established place in medical treatment as a useful supplementary source of the B group of vitamins. Bakers' yeast is also used, but is generally less rich in thiamine. Brewers' yeast has a bitter taste and so is difficult to take in nutritionally significant amounts. Another species, ' food yeast ' (*Torula utilis*), is more acceptable.

In Great Britain the Distillers Company Ltd. (D.C.L.) produce a dried autolysed yeast in which the protein is largely broken down into its constituent amino acids. Various protein-free yeast extracts (*e.g.* Marmite, Vegex) are also available, which are pleasant to take either in soups or stews or as sandwich spreads.

CHAPTER 22

PRESERVING, COOKING AND WASTAGE

1. PRESERVING

THE art of preserving food is an essential of civilisation. Without it life could be no more than an elemental struggle for day-to-day survival. From time immemorial in every small farmstead foods have been stored and preserved by domestic methods which include drying, smoking, jam-making, pickling and bottling. With the industrial revolution, when huge populations became completely separated from the sources of their food supply, these homely methods became extended and have developed into the large industry of modern food technology. This includes the canning, dehydration and refrigeration industries. Preservation by irradiation is on trial in the U.S.A. (Robinson, 1959). Food industry is a logical development of household science and essential for any industrial population.

How do these numerous and complex methods of food preservation interfere with the nutritive value of foods? This is obviously a most important question and fortunately we can answer it clearly and definitely: very little. It is a cardinal point of food preservation known equally well to the housewife and the food industrialist that only foods of good quality can be preserved effectively. In consequence all preserved food must be in good condition in the first instance and superior to much of the food that is sold and consumed fresh. This applies especially to perishable foods such as fish and vegetables. Further, another broad generalisation is possible; the essential nutrients of food are chemically more stable than the flavouring substances. Hence any preserved food which maintains its original taste and flavour is likely to have retained its nutritive value. The one important exception to this generalisation concerns ascorbic acid. Losses of ascorbic acid in the processing of foods may be large. Dried fruits and vegetables, for instance, often have little or no vitamin C activity: yet canned or frozen fruits generally contain most of the vitamin present in the original fresh fruit. Nevertheless it is unwise to rely solely on preserved foods as a source of this vitamin. A daily supply of fresh fruit or vegetables is desirable.

The general statement that the losses of essential nutrients in canned foods are small is supported by a great mass of chemical analyses. It also receives support from biological experiments. Godden and Thomson (1939), for instance, bred and fed rats over a period of 18 months, through four generations, on a diet consisting entirely of canned food. Their performance in respect of breeding, growth and composition of the body as a whole—as well as of the bones and teeth separately—was in all respects comparable with that of similar rats fed on a diet of corresponding foods, bought in the shops or grown locally. Similar evidence is difficult to obtain for man, but these experiments taken in conjunction with chemical analyses leave little room for doubt that dependence on preserved foods is not deleterious to health. This is an important point for health education; housewives and others are often unnecessarily suspicious of the value of canned foods.

2. COOKING

All civilised men cook their food—or perhaps more accurately get their womenfolk to cook it for them. The cooking of food has three advantages: (1) the food is made more palatable and appetising, (2) it becomes more easy to digest and (3) is made more hygienic. We are not qualified to discuss the techniques necessary for (1). It must suffice to say that cooking is one of the most important and agreeable of the human arts; all the dietary advice that a physician or dietitian gives to a patient may well be useless unless supported by the art of a good cook. Cooking effectively removes most pathogenic organisms from food, but they may be added again by a cook who is unclean in her person or habits. Food hygiene is more fully discussed in the next chapter.

Effects of Cooking on Digestibility

Most foods of animal origin could probably be digested raw by man, but raw meats are unpalatable and seldom consumed; yet in a crisis a hungry man will readily eat the raw flesh of any beast, bird or fish. The cooking of meat makes it easy to chew and so allows the digestive juices a more rapid access to the protein. The heat of cooking coagulates the muscle proteins, which actually thus become less readily digested by proteolytic enzymes *in vitro*. But the tough collagen fibres of connective tissues are converted by heat into gelatin and this increases the tenderness of the meat. The elastic tissue in tendons and sinews is insoluble and virtually indigestible.

Fruits and green vegetables may be eaten raw in limited amounts. Cereals, roots and pulses, however, cannot easily be digested by man unless cooked. Most plant cells are surrounded by a tough cellulose wall which is little disrupted by mastication and through which the digestive enzymes cannot readily pass. The heat in cooking causes the starch within the cells to swell. This bursts the cell walls and the starch and other nutrients within them become accessible to the digestive enzymes.

Effects of Cooking on Fats

Heating fats to over 250° C. may cause important chemical changes. Many experiments have shown that heated fats can be toxic to rats. The subject has been reviewed by Brown (1959). He states that the conditions under which the changes in the fat were produced experimentally were far more drastic than would normally occur in kitchens, either in restaurants or homes. However, it is sensible not to overheat fats and not to use them too long for deep fat frying. There is no evidence that the occasional use of fats damaged by heat has any permanent effect on health.

COOKING LOSSES

A full account of this subject, with the results of many analyses, is to be found in papers by McCance and Shipp (1933) and McCance *et al.* (1938). A useful review has also been provided by Stewart (1946).

Losses occur in two ways. First, nutrients may be leached out of the tissues of either plant or animal foods and discarded in the cooking water. Losses of minerals and water-soluble vitamins may result. Secondly, the heat may destroy some of the vitamins present.

Far and away the most important of these losses occurs in the preparation of rice. The method of preparing the rice may determine whether or not the cooked product retains sufficient water-soluble vitamins to prevent beriberi. Rice, as purchased in any bazaar, has to be washed and this washing water must then be discarded. The rice is then cooked in water and this cooking water is usually discarded, though it is sometimes consumed. Table 22, 1 shows that the losses of thiamine particularly may be very high. Similar losses of nicotinic acid also occur. It is probably a safe assumption that for rice half of the water-soluble vitamins which escape the millers are washed away by the housewife and so lost to her family. This can only be a rough approximation ; sometimes losses in the kitchen may be less ; frequently they are much more. The importance of reducing these losses by the use of the smallest possible amount of water, both for the washing and cooking of rice, cannot be overstressed. This lesson is a most important point in the education of housewives throughout all rice-eating countries.

TABLE 22, 1. *Thiamine content of Javanese rices*
(mg./100 g.)

	Husked, not milled rice	Undermilled rice	Polished rice
In original condition . .	0·24–3·0	0·15–0·24	0·06–0·12
After washing . . .	0·15–0·18	0·08–0·12	0·06
After prolonged washing .	...	Well below 0·06	Well below 0·06

Data of Van Veen, quoted by Aykroyd *et al.* (1940).

Considerable quantities of water may be used in the cooking of fruits and vegetables. This may extract an appreciable proportion of the minerals and water-soluble vitamins present in the raw foods. The concentration of these nutrients in fruits and vegetables is so small that the total losses in the cooking water are not nutritionally significant except in the case of ascorbic acid, as discussed below.

All meat loses weight when it is cooked. The losses may vary from 10 to 40 per cent. of the initial weight, being greater with roasting than with stewing (Andross, 1946). A large proportion of this loss is water, part of which forms *gravy* which contains water-soluble vitamins, minerals, nucleic acids and protein. Most of this is usually consumed, but some wastage occurs.

The heat employed in cooking inevitably causes some destruction of vitamins, but of course does not affect the minerals. The fat-soluble vitamins are fairly stable to heat. Carotene and vitamin A are not destroyed in significant amounts at the temperature of boiling water. With the higher temperatures used in frying losses are also small, provided there is a limited access to air. Most of the fat-soluble vitamins are preserved in deep frying. But if a shallow frying pan is used, the combined effects of the heat and the free access to air may cause the complete destruction of vitamin A.

Of the B group of vitamins, thiamine is the most sensitive to heat and in some cooking processes up to 30 per cent. may be destroyed. This is seldom of nutritional significance. As removers of thiamine, cooks are not in the same class as the millers.

Ascorbic acid is the one important nutrient of which losses in the kitchen may be large and significant. Ascorbic acid is readily oxidised and, if this proceeds beyond the stage of dehydro-ascorbic acid, all vitamin activity is permanently lost. Oxidation may be accelerated by enzymic action, by heat, by an alkaline medium, by traces of copper and by free access to atmospheric oxygen. These facts have practical application in preserving and cooking.

In most plant tissues there is an enzyme, ascorbic acid oxidase, which is separated from the ascorbic acid in the intact cells. When leaves or fruits are bruised, pounded or chopped, cell structures are damaged and the enzyme gains access to the vitamin and begins to destroy it. However, the enzyme is rapidly inactivated at temperatures of 60° C. and above. The destruction of ascorbic acid is minimal when fruits and vegetables are immediately placed in boiling water, but maximal if they are placed in cold water and slowly brought to the boil. Some loss of the vitamin is inevitable in cooking, but can be reduced if the cooking is carried out for the shortest possible time. Access to oxygen can be eliminated if the water is first boiled to drive off dissolved oxygen and if a lid is placed on the saucepan to exclude air. Copper pots should never be used for cooking vegetables ; also baking soda should not be added to preserve their colour. Similarly when potatoes are fried, losses of ascorbic acid will be less when they are rapidly immersed in hot deep fat than when they are cooked slowly in a shallow frying pan. The losses due to heat will continue if vegetables or fruit are kept on a hot-plate after cooking and not served immediately. Ascorbic acid is very soluble in water, and the more cooking water used, the greater the amounts of the vitamin that will be leached out and discarded.

If all these rules are disobeyed—as they frequently are in many homes and perhaps even more often in canteens—vegetables and fruits may be served almost devoid of the vitamin. This particularly applies to potatoes, often the most important source of ascorbic acid in the diet. Thompson (1946) has shown that less than 30 per cent. of the vitamin that survives cooking may be retained after a period on a hot-plate in a canteen. However, if the proper precautions are all taken, it is possible to preserve as much as 70 per cent. of the ascorbic acid. In the absence of any accurate knowledge of the cooking methods used, it is advisable to assume a destruction of 50 per cent. of the vitamin.

In recent years small domestic pressure cookers have been increasingly used in many homes. In these the temperature may be raised well above the normal boiling point, but the time of exposure to heat is greatly reduced. These two effects tend to cancel out. Potatoes cooked in a pressure cooker have been shown to retain 80 per cent. of their ascorbic acid. There is no evidence that pressures up to 15 lb./sq. in. cause any increased loss of the vitamin and such cookers may be used with confidence.

Similar rules apply to bottling both fruit and vegetables, whether in the home or in a factory. With the best techniques modern factories are able to preserve nearly all the antiscorbutic activity of the fresh food in bottling, freezing or canning.

3. WASTAGE

Physiologists who attempt to assess human needs for nutrients naturally use as their basic data measurements of amounts of food that are actually eaten. On the other hand the basic data of food administrators, whose duty it is to see that a country or district has sufficient food to satisfy physiological requirements, are the statistics of the size of the crops in the fields and of the amounts of food in the holds of ships in the ports and in railway wagons at the frontiers. These two sets of data cannot be directly compared, for it is inevitable that a proportion of the food crop in a field or of a cargo of food in a ship will never be eaten but will be wasted.

Wastage may occur at various levels. First, there is the wastage between the farms and the retail shops. With good transport facilities, well-equipped stores and modern industrial plant, wastage here should be very small. But if such facilities are inadequate—as they often are in many countries—losses may be great. Rodent and insect pests may be responsible for enormous losses; bacterial and fungal contamination may also contribute, if storage conditions are not both dry and cool. Published figures for national food supplies usually include a deduction for wastage on farms, in processing and in distribution. Tables in the annual reports of FAO (Food and Agriculture Organisation of the United Nations) set out for each country the ' retail level ' of available food supplies, the nutritional value of the food as it passes across the grocer's counter. When calculating the nutrient content of such foods ' as purchased ' allowance is made for inedible portions—the bones of meat, the peelings of roots and tubers.

Secondly, there is wastage in the home. This may be due to (1) spoilage, associated often with bad storage facilities, (2) losses in cooking, of which some is inevitable, (3) food fed to domestic animals and pets and (4) plate waste. Very little actual data is available for assessing these losses. An FAO report (1957*a*) states : " No single figure for waste can be universally satisfactory. The available data indicate that in most countries edible food waste does not exceed 10 per cent. of the calories at the retail level." This figure is certainly too high for communities living at or near the hunger level. Anyone who has been a prisoner-of-war can relate elaborate precautions taken to prevent any loss of the meagre rations and may describe how the men habitually licked their plates clean. Similarly in many poor homes, especially in Africa and Asia, nothing is wasted.

By contrast, in the homes of some of the rich, waste may be enormous. Inspection of the swill-cans in wealthy districts has led to estimates of waste up to 500 Cal./head/day. Clearly any overall national assessment of household waste can only be a guess.

The important point is not to compare a national figure for the supply of available food directly with an assessment of physiological needs. This is an error that has frequently been made in the past. Food supplies must be significantly higher than physiological needs in any country. A retail supply of 10 per cent. more than physiological needs should ensure against both undue hardship and careless waste.

Similarly, in setting out ration scales for institutions, armed services, expeditions, etc., an allowance of 10 per cent. in excess of estimated physiological needs will usually represent a proper compromise between kindly care and prudent economy.

CHAPTER 23

FOOD POISONS: (1) INFECTIVE AGENTS

No account of human nutrition would be complete without some reference to the fact that food may be a source of harm as well as of benefit to the body. Every person concerned with providing proper food for others should be aware of the various harmful agents that food may contain and know how to avoid them. Broadly speaking, such agents may be classified under the three headings of infective agents, chemical agents and natural food poisons. These are considered in turn in this and the following two chapters.

BACTERIAL FOOD POISONING

Definition.—Food poisoning is a difficult term to define; through common usage it is accepted as meaning an acute gastro-enteritis developing some hours (up to 48) after the consumption of unwholesome food or drink. It is customary not to include under this term (*a*) such specific infectious diseases as enteric fever, dysentery and cholera which are also spread by infected drinking water and food, because their incubation period is longer and gastritis is not an essential feature; (*b*) food idiosyncrasy or food allergy, since the food ingested is wholesome (*e.g.* shellfish), but the patient's reaction to it is abnormal; (*c*) digestive upsets resulting from the eating of food which is too rich (*e.g.* fat), or mechanically irritating (*e.g.* unripe fruit). Children are particularly prone to such upsets.

Ætiology.—In contrast to typhoid fever which is rarely encountered in Great Britain at the present time, a remarkable increase in the reported incidence of food poisoning as defined above has occurred during the past few years. This disease has recently been made separately notifiable in Great Britain, with the result that some estimate can now be given of its frequency, together with the most usual causes. The evidence has been well reviewed by Cowan (1955). The most common cause is the salmonella group of organisms, with staphylococci far behind in second place. This may be partly due to the difficulties of tracing the poisonous effects of staphylococci once the organisms themselves have been killed by cooking, while their heat-resistant toxins remain in the food. In the U.S.A. staphylococci are apparently the most common offenders. It is noteworthy that in more than half the outbreaks of food poisoning cited by Cowan the cause was never discovered, partly perhaps from lack of bacteriological resources to detect the original infection. In other unexplained cases the cause may have been a virus infection or indeed some non-infective cause, as discussed in the following two chapters. A useful symposium on food poisoning and its prevention was held by the Nutrition Society with one of us in the chair (Nutrition Society, Scottish Group, 1957). A full account of the ætiology of food poisoning and of the responsible organisms is given in a publication by the Royal Society of Health (1962).

Bacterial food poisoning is usually divided into two main groups (1) the *infectious* type, and (2) the *toxic* type.

Infectious Type

The organisms mainly responsible belong to the Salmonella group. *Salmonella typhimurium* has been found to be the organism causing at least three-quarters of the cases of food poisoning of the ‘ infectious ’ type in Great Britain.

The salmonellas as a group gain entrance to the human body in food which becomes infected when contaminated with fæces or urine containing the organisms. Such infected excreta may come from another human being suffering or convalescent from a salmonella infection or, occasionally, from a chronic, symptomless carrier of the organisms. It should be remembered however, that other animals, notably rodents, poultry, pigs, cats and dogs can also be important reservoirs of salmonellas. *Sal. typhimurium* (otherwise known as *Bact. ærtrycke*) is a natural pathogen of rats and mice. These vermin may leave infected droppings or urinate on food exposed in stores and kitchens. In common with other salmonellas, *Sal. typhimurium* may also be present in eggs, especially those of ducks, and may not be destroyed in the ordinary process of boiling.

It is important to note that the size of the infecting dose of bacteria bears a close relationship to the speed of onset of symptoms and to the severity of the illness. This indicates clearly the dangers of bacterial multiplication which may take place when food is exposed to infection and thereafter remains at a warm temperature, as in a kitchen, for many hours or even days. The types of food which are particularly likely to be infected are twice-cooked meat dishes, stews, gravies, soups, custards, milk and synthetic cream ; also tinned foods which, though usually initially sterile, may become infected if not consumed immediately after the tin has been opened. While hens’ eggs are very rarely infected, ducks’ eggs are quite commonly so because the duck is a carrier of Salmonella organisms in its oviduct and alimentary tract. Hence ducks’ eggs are not suitable for the preparation of lightly cooked foods such as custards, milk puddings, etc., because it has been shown that boiling for 10 to 15 minutes is necessary if sterilisation is to be secured.

Experience has shown that outbreaks of food poisoning are especially liable to occur whenever large amounts of food are prepared and when the remaining food not consumed is kept for future meals. The danger of infection is greatly increased if such food is kept at a warm temperature instead of being stored in a refrigerator. It is not surprising therefore that food poisoning is reported far more frequently from canteens, restaurants, hospitals and other institutions than from private homes.

Toxic Type

The organisms mentioned above exert their ill-effects by virtue of their ability to gain entrance to the human digestive tract and multiply there to the detriment of their host. Other bacteria may grow in food during the process of storage and preparation, producing, in the course of their metabolism, excretory products (exotoxins) that are highly toxic to the subsequent human consumer. The chief organisms concerned are discussed below.

The Staphylococcal Group are often present in the upper respiratory passages of man and on the surface of the human body, where they may produce boils and other infections. Food may be infected if coughed upon or handled with dirty fingers ; meat in particular, when cut up to make pies and other composite dishes, is an ideal medium on which a heavy growth of the organisms may develop, with the production of toxins. Subsequent sterilisation of the food by cooking will destroy the bacteria, but the toxins are heat-stable and can still cause food poisoning. The source of the infection is often very difficult to trace since the bacteria, being dead, can no longer be cultured from the suspected food. Likewise, the commercial preserving of foods such as meat and milk, while it stops all subsequent growth of staphylococci, does not destroy their toxins ; consequently such foods may cause food poisoning if improperly handled before they reach the factory. Staphylococci are the most common cause of food poisoning in the U.S.A.

Botulism. *Clostridium botulinum* grows in organic matter in the absence of oxygen, producing a most powerful and deadly toxin. It occasionally gains entrance to human food and, if it has a chance to grow, either before or after the food is cooked, it subsequently produces severe food poisoning which may be fatal. Fortunately it is very rare ; 0·01 mg. or less of its toxin may be fatal to a man. Botulism was the cause of the celebrated Loch Maree disaster in which eight people died in 1922 after a picnic. Their sandwiches had contained ‘ wild duck ’ paste.

The Gas Gangrene Group (Clostridia) were originally identified as the cause of gas gangrene. It has since been realised that they quite commonly grow in food (especially meat) awaiting cooking, producing toxins which may subsequently cause food poisoning.

Streptococci, both hæmolytic and non-hæmolytic varieties, may cause food poisoning.

OTHER PATHOGENS SPREAD BY FOOD

In addition to the organisms causing classical food poisoning as discussed above, there are many living agents (bacteria, spirochætes, protozoa and worms) which may gain entrance to the body through infected water or food and cause a variety of illnesses.

BACTERIA

Typhoid and Paratyphoid Fevers (The Enteric Fevers)

The agents responsible for these diseases belong to the Salmonella group of organisms. The enteric fevers have a world-wide distribution and occur endemically wherever sanitation is poor and the water supply is likely to be contaminated with sewage. In such regions flies also play a part in the transmission of these diseases. In Great Britain typhoid fever is usually spread by carriers who infect other people by contamination of food, milk or water. Occasionally infected shellfish or watercress is responsible for an outbreak.

The Dysentery Group (Shigellæ)

This group of bacteria are the organisms responsible for bacillary dysentery—so common in hot climates where the sanitation is primitive. Although drinking water (or uncooked foods washed in it) may be the medium by which these organisms gain entrance to the body, flies are the commonest cause ; if flies feed on the exposed excreta of people suffering from dysentery, they may then transfer their attentions to exposed food and so spread the disease.

Cholera

This dreadful disease is due to a *vibrio* that is transmitted from one patient to another almost entirely in drinking water contaminated with human fæces. It occurs in epidemics, producing intense and often fatal diarrhœa. Cholera was confined to China and Bengal for many centuries until 1817 when, for some obscure reason, it suddenly broke loose and spread in pandemic form throughout the travelled world, striking particularly those communities with defective sanitation. It took about 15 years to reach Scotland ; travelling across India, into Russia it reached the Port of Leith from Riga in 1832. Its rapid spread in the insanitary ' lands ' of Edinburgh's Royal Mile caused great alarm, hastening the evacuation to the New Town and leading to the appointment of the first Medical Officer of Health. When it reached the plantations of the Southern States of the U.S.A. the slaves called it ' collywobbles '—a corruption of *Cholera morbus*—which remains a nursery euphemism for diarrhœa until this day.

SPIROCHÆTES

Leptospirosis hæmorrhagica is the organism responsible for Weil's disease which is characterised by hepatitis which may be mild or moderate, or so severe as to be fatal. The organism is carried by rats whose urine may infect human food. The organisms may also gain entry to the body via the skin and mucous membranes. Cases of this disease have occurred among those who used to gut fish in rat-infested premises in Aberdeen (Davidson & Smith, 1936). It also occurs among coalminers, sewer workers and farm workers. Many cases have occurred in Queensland, Australia, among workers in sugar cane plantations.

PROTOZOA

The chief offender of this group is the entamœba that causes amœbic dysentery. It is transmitted from one infected person to another by water contaminated with human fæces or by foods such as raw vegetables.

WORMS

Various parasitic worms gain entrance to the human body through the medium of food or water. It is beyond the scope of this book to review their natural history and the pathology they create ; the reader should consult a textbook of medicine for details ; but a brief summary of the most important species, and the means whereby they infect the body, seems appropriate here.

Tapeworms.—These parasites have a curious life-cycle. The adult worm lives in the gut of an animal. Egg-laden segments break off and are passed in the fæces. The eggs then lie where they are excreted until they chance to be eaten by another animal (usually of a different species) which becomes the ' alternative host.' Generally the eggs perish ; but if the new host is the right species, they hatch out into larvæ which penetrate the gut wall and finally develop into cysts (cysticerci) ; these may lodge in the muscles, brain or liver. There they remain until these organs chance to be eaten by an animal of the previous species, when one cyst at least may have the fortune to gain a foothold in the gut, and develop into an adult worm. It follows that tapeworm infestation is essentially a disease of carnivorous animals, and the alternative host is usually some vegetarian animal on which it preys and which is likely to eat food contaminated by its fæces. Man, being a carnivore, usually acts as the unwilling host to the adult worm in his gut. But more rarely he may acquire the cystic form of the infestation.

The tapeworms of importance to man are as follows :

Tænia solium.—The alternative host for this worm is the pig ; man acquires the adult worm from eating ' measley pork ' infested with cysts. The Biblical ban on eating pork no doubt arose from the intuitive knowledge that too much association with pigs may be dangerous to health.

Tænia saginata.—The adult worm of this species is acquired from eating the infected meat of cattle.

Diphyllobothrium latum.—This interesting worm occurs sporadically among the inhabitants of Scandinavian countries. It gives rise to a conditioned vitamin B_{12} deficiency. The alternative host is provided by sea fish which feed on infected human sewage.

Man may occasionally become infected with the cystic stage of tapeworms. The species most concerned is *T. solium.* In New Zealand the dog-sheep tapeworm has been reported as an occasional cause of cysticercosis in man. The shepherd finding the liver of a dead sheep full of cysts feeds it to his dog, which thus acquires a tapeworm. The dog's fæces contaminates the playground of the children, who thereby run the risk of developing cysticercosis.

Ascaris (roundworm).—This large worm, widespread throughout the world, needs no alternative host and is transmitted from man to man in food or water contaminated with fæces containing its eggs.

Trichinella is a minute worm that sometimes lies encysted in the muscles of the pig. When the live cysts are eaten by man the worms invade his muscles, producing acute pains, fever and often a severe conjunctivitis.

Threadworms infecting the lower bowel are a common cause of anal irritation in children. They gain entrance in food contaminated with infected human fæces and their presence is a reflection of the standards of hygiene observed by the mother.

Hookworm (Ankylostoma) and **Bilharzia (Schistosoma)** are two other species of parasitic worms which infect man through the medium of water contaminated with human fæces. But they gain entrance to the body through the skin (usually of bare feet) rather than through the gut. Hookworms pass via the blood stream and lodge in the upper intestine; they produce a ' conditioned ' iron deficiency anæmia (Chapter 44). Bilharzia lodge in the lower bowel, bladder or liver, producing chronic, debilitating granulomatous inflammation.

FOODS AS A SOURCE OF INFECTION

Milk

Milk is an excellent food not only for man but also for bacteria, for it forms an almost ideal culture medium for their growth. Once inoculated with bacteria it can become a highly dangerous source of infection, particularly if allowed to incubate in warm surroundings for some time before it is used. Organisms may find their way into milk from the dirty udders of cows, the dirty hands of milkers, dirty pails or bottles (Plate XXVI), from ' droplet infection ,' an infected person coughing over the open pails or from flies settling on their sides. Apart from the common organisms of food poisoning—salmonella and staphylococci—milk may be a vehicle for the transmission of the organisms of tuberculosis, diphtheria, scarlet fever, streptococcal sore throats and undulant fever. Indeed dirty milk is a major health hazard in all climates. For milk to be safe it should be collected, bottled and distributed under rigid hygienic conditions. When milk from many sources is pooled, as is often necessary in supplying large towns, an infection introduced from a single sick cow or milker will contaminate the whole supply. The most certain way of eliminating this danger is to pasteurise all milk handled in bulk immediately before it is bottled, dried or otherwise prepared for use. Another useful means of reducing the risk of bacterial infection in milk, particularly in hot climates and where the supply is small and locally produced, is to inoculate it deliberately with a culture of the *Lactobacillus acidophilus* (Chapter 20).

Meat

Not only can meat contain the encysted forms of worms, but the carcass may quickly develop a growth of gas-grangrene organisms (*Clostridia*) producing dangerous toxins if it is not cleaned and treated soon after slaughter. Meat that is cut up and left in a warm place forms an excellent culture medium for the growth of pathogenic bacteria which are easily introduced into it by flies or dirty human hands. Consequently made-up meat dishes such as pies, mince, curries and sausages are the most frequent cause of food poisoinng.

Fruit and vegetables

By contrast, fruit and vegetables are a relatively poor culture medium for the growth of pathogens. Even when infected with food-poisoning organisms, the growth is seldom heavy enough to cause any upset in the consumer. When fruits such as grapes and apples, or roots of various kinds, are deliberately allowed to grow micro-organisms, as in the preparation of alcoholic drinks, the predominant growth is usually that of yeasts which discourage the growth of bacteria harmful to man. The product is therefore relatively innocuous.

Pathogenic organisms are unable to thrive within living plant tissues; consequently, in contrast to dead meat, if they lie on the surface only they can be washed off. Provided fruit and vegetables are fresh, sound and properly washed before use, they present little danger if sanitary conditions are satisfactory. However, fruits and vegetables can become infected by flies, especially when lying about unprotected in shops in the summer. Lettuces and other salad vegetables may act as carriers, especially of amœbæ and ascaris, if manured or watered with infected material. In hot climates it is well to avoid soft fruits, individually picked by dirty hands, and to prefer fruits with a skin that is peeled before eating.

Bread and other cereals

Fortunately bread and other cereals are poor culture media for bacteria. They are usually too dry. However, danger may arise from cereals that have been contaminated by the excreta of rats or mice and are subsequently eaten without adequate sterilisation by cooking.

TREATMENT

Acute gastritis and diarrhœa, arising from food poisoning, should be treated along the lines described on pages 503 and 504 in the same manner as when these conditions arise from other causes. In addition, if the nature of the infecting organism is known, the appropriate antibiotic, antitoxin, vermifuge or other specific remedy should be used.

PREVENTION OF DIETARY INFECTIONS

The counsel of perfection is to eat only foods that are grown, gathered, stored and cooked under conditions remote from any possibility of contamination with the excreta of men or animals. Drinking water should also be wholly free from such contamination. Undoubtedly the introduction of drains, which separated the sewage from the drinking water, was the greatest single measure taken by the human species for the preservation of its own health. But the perennial problem has been, what to do with the sewage afterwards ? To dump it into the sea is wasteful, since it deprives the land of much-needed nitrogen and other nutrient elements. The other practicable alternative, in cities at least, is to collect and treat the sewage until all pathogenic organisms, together with their spores or eggs, have been destroyed by other (harmless) organisms and only then to return it to the land. But the sewage plant necessary for such treatment is often prohibitively expensive ; moreover, it is impracticable to install it in scattered rural communities. For the isolated farming community the septic tank is a useful partial solution ; but when its contents are periodically dug out and returned to the land, they are not always wholly free from pathogens which may subsequently infect the farm worker.

The problem of sewage disposal is always more serious in hot climates since many pathogens survive well in warm soil or water. The eskimo who defæcates on an ice floe is no danger to his neighbours, whereas an arab, who relieves himself into running water, may easily pollute the local drinking water. It is indeed fortunate that man is born with an innate distaste for the sight and smell of other people's excreta ; the only misfortune is that our senses are not sharper, so that we could always detect food that is contaminated. Too often the sewage that finds its way into food and water is too diluted to offend our senses and yet still highly infective. The only practical solution is to use imagination as a sixth sense to envisage the organisms that may be present in foods grown and produced under insanitary conditions and, when necessary, to obtain the expert help of a bacteriologist or sanitory inspector.

Meat is always a possible danger and should be routinely inspected before being passed fit for human consumption. The expert eye of the sanitary inspector can detect worm infestation, or the growth of gas-gangrene organisms which may subsequently produce toxic food poisoning.

Wherever the sanitation is primitive and particularly in hot climates, it is wise to assume that all food is contaminated unless proved otherwise and to adopt a few simple rules to avoid possible dangerous consequences.

1. **Choice of food.**—Select local foods of local origin that are produced under the best conditions that circumstances will permit, *e.g.* vegetables

grown in one's own garden, are always safer than those bought in the bazaar or market.

2. **Storage of food.**—All food should be stored in the coolest place available, free from flies and vermin. The ancient processes of drying, salting and pickling all help to discourage the growth of pathogenic organisms. Far more effective is the modern process of refrigeration. Facilities for low temperature storage should be adequate in all restaurants and institutions in which food is cooked in large quantities, and which may have to be kept for hours or days before being consumed.

3. **Kitchen staff.**—Those who handle food should be taught rigid rules of personal hygiene and should be under medical supervision to see that they do not suffer from worms, staphylococcal skin infections, open tuberculosis or other possible causes of infection.

It is an essential duty of all those responsible for the handling and preparation of food to see that their staff have proper, fly-free lavatories or latrines, and that clean water, soap and towels are provided nearby so that hands may be washed routinely after defæcation.

4. **Preparation of food.**—Water used for cooking, drinking or washing food should be sterilised by boiling if its purity is in doubt. All foods that are eaten raw, such as fruit and salads, should be carefully washed immediately before consumption. Some authorities recommend the addition of a little potassium permanganate to the water used for washing. Food that is cooked should be maintained at a sufficient temperature long enough to ensure the death of any pathogens that it may contain. The time and temperature needed varies very much from one food to another. For instance, milk can be sterilised by the process of pasteurisation which maintains it at 72° C. for 15 seconds. This process has the advantage that it does not curdle the protein of milk. But when an infected duck's egg is boiled for the usual 4 minutes, *Sal. typhimurium* may survive the process. Likewise, beef or pork that is grilled ' rare,' *i.e.* subjected only to a brief intense heat on the surface, may contain viable cysts of worms in the interior of the steak. It should be remembered that ordinary methods of cooking do not destroy staphylococcal and clostridial toxins.

With proper precautions, however, there is no reason why people living almost anywhere—even under hot, primitive conditions—should not enjoy a full, varied, pleasant, safe and nutritious diet using locally produced food without too much reliance on expensive, imported canned foods. To avoid all indigenous fruits and vegetables from fear of being infected by them is unwarranted.

Conclusion.—The means of preventing food infections has been succinctly stated by Oldershaw (1955): " Clean food handled by clean people in clean premises with clean equipment, and protection of food from flies and vermin."

CHAPTER 24

FOOD POISONS: (2) CHEMICAL AGENTS

IN the past all people depended for survival on the food grown in their immediate neighbourhood and large numbers still do. Agricultural labourers still comprise the greatest part of the world's population and their health and well-being is determined in many countries by the ability of the local soil to produce enough calories (usually in the form of cereals or starchy tubers) and enough essential nutrients provided by such foods as milk, eggs, meat, fish and fresh vegetables. One serious effect of the Industrial Revolution during the last century was to congregate large numbers of people in towns, far removed from the immediate source of their food. Attempts were made at first to overcome this difficulty by trying to perpetuate a *rus in urbe*. Even in this century, milk-producing cows and egg-laying hens were still tended within ' the great wen ' of industrial London. But realisation of the dangers of bacterial infection among people living too close to the source of their food finally discouraged the production of food in crowded cities. The provision of an alternative supply of clean food raised a new problem, and incidentally created a new and major industry. The townsman of to-day depends increasingly for his nutritional health on a vast industry of food production, preservation and distribution which is usually controlled by private enterprise, though in times of crisis (*e.g.* in Great Britain during the 1939-45 war) governments have found it necessary to intervene. The nutritional well-being of the newly established and rapidly increasing urban populations, especially in the tropics, is seriously impaired through lack of adequate application of food technology. Here governments, with the help of commercial interests, if necessary, from abroad, must encourage the development of suitable local food industries as quickly as possible. The Food and Agriculture Organisation of the United Nations is assisting governments in many parts of the world to train local personnel in food technology.

The successful supply of an adequate diet for city dwellers in the more developed countries has been a remarkable example of industrial achievement, made possible by the scientific development of food technology. The first problem was to preserve the quality and appearance of the food so that it would be acceptable to the purchaser. It is not surprising that every chemical art and aid has been invoked during the development of this industry. An entertaining and informative account of modern food technology has been written by Pyke (1952).

Almost inevitably the food industry had its growing pains; it arose rapidly, before either doctors or chemists realised or could appreciate the toxicological problems involved. In the early days of industrial expansion there was a great temptation to earn quick profits by supplying the townsman with any food that he would accept. Since little was then known of nutritional science, and there was no control over the quality of food put on the market, it was possible to adulterate food in any way that would help to sell it profitably in larger quantities. The first editor of the *Lancet*, Dr Wakley, led a crusade against this practice. Beginning in 1851 he published in his journal the names of over three thousand tradesmen whose wares had been found, by a privately sponsored investigation, to be adulterated. Many cautious people at the time were sure that the *Lancet* was doomed because the costs in libel actions would kill it. Yet Dr Wakley was never sued effectively by any of the people whose inferior products he exposed, chiefly because he was supported by the weight of contemporary medical opinion. The individual initiative of Dr Wakley led ultimately to a series of Food and Drug Acts passed by the British Parliament and subsequently adopted with various modifications by other countries. The force and power of these Acts was gradually increased in the light of later and sometimes bitter experience. There was, for instance, the beer-poisoning tragedy in Manchester at the turn of the nineteenth century ; six thousand people were poisoned and seventy died from drinking beer brewed from sugars that had been derived from vegetable cellulose by the action of sulphuric acid. Unfortunately someone had forgotten (or did not know) that crude sulphuric acid contains arsenic. In the U.S.A., in a similar irresponsible manner, *tri-ortho*-cresyl phosphate was arbitrarily introduced in the preparation of ' Jamaica Ginger.' The effects of this powerful neurotoxin came to be known as ' Jake Paralysis.' In September 1959 in the town of Meknes in Central Morocco there occurred suddenly a paralysing disease of unknown origin. At least 2,000 people were paralysed to a greater or lesser extent. The cause was shown to be poisoning by *ortho*-cresyl phosphate, present in lubricating oil, which had been sold as ' olive oil.' Smith and Spalding (1959) who were sent by WHO to advise the Moroccan health authorities give a good account of the disaster.

To-day the big industrial firms who cater for the nutritional needs of city dwellers are generally acutely aware of their responsibilities and employ suitable teams of chemists, biochemists and bacteriologists to ensure that their products conform, at the very least, to the standards that the law and public opinion expect. Yet despite this care, unknown hazards arise and there are still possible dangers from the chemical sophistication of food. These dangers may be divided into two categories —accidental and deliberate.

THE ADDITION OF CHEMICALS TO FOOD

Accidental Adulteration

It is now rare for food poisoning to be reported as resulting from the accidental addition of chemicals, though in the last century such accidents were comparatively common. The arsenical poisoning in the Manchester beer case has already been mentioned. Another common metallic poison was lead. Lead in the solder of the earliest tin cans used in the canned food industry was liable to solution by acid fruit juices, sometimes with poisonous consequences. Lead poisoning (plumbism) was not uncommon when lead pipes were used to supply drinking water, especially if it was unusually soft. The use of lead pipes for drawing beer from the cellars of public houses was a similar danger. It used to be the ' regular customer,' calling in for his pint at opening time, who drank the first full dose of lead from the beer that had been lying in the pipes overnight. Even to-day the water of old houses may still be supplied in lead pipes. Recently a man was admitted to hospital in the Midlands of England with acute lead poisoning. After following several false trails Whitehead and Prior (1960) discovered the source of the lead. It was an earthenware bowl, over one hundred years old, in which the patient regularly made elderberry wine. The bowl was glazed with a soft lead glaze which was cracked and pitted by the acidity of the wine. If the local water is soft, without sufficient calcium and magnesium salts to coat the lining of lead pipes, it is a wise precaution to run the tap for a while before withdrawing water to infuse the early morning cup of tea.

Accidental chemical poisoning occasionally occurs in the home, *e.g.* when the harassed housewife absentmindedly picks the wrong bottle, using rat poison or weed killer in mistake for baking powder or cream of tartar. It is still necessary to emphasise that all poisonous chemicals used for domestic purposes should be properly labelled and kept as far as possible from the kitchen.

Insecticides, fungicides and weed killers

For many years compounds of arsenic and copper, such as Paris Green and Bordeaux Mixture, have been sprayed on crops to kill insects. These metallic poisons, when used in the dilute solutions recommended by the manufacturers, have little toxic effect on man. In recent years a large number of entirely new organic compounds have been produced as aids to the farmer in his perennial battle against weeds, insects and rot-producing fungi. The best known of these is DDT. So far no definite ill-effects have been reported from the accidental contamination of foodstuffs with this compound. Nevertheless it should be remembered that DDT is highly soluble in fats and tends to accumulate in the fat stores of the body ; the possible long-term effects of this accumulation have yet to be determined. More dangerous, from the standpoint of possible short-term effects, are certain organic phosphates. These are most effective insecticides by virtue of their power of inhibiting the enzyme cholinesterase. Unfortunately, however, man needs this enzyme just as much as does the Colorado beetle. These organic phosphates in fact are akin to the ' nerve gases', the use of which as agents of chemical warfare would compete with the hydrogen bomb in horror. Isolated cases of poisoning by organic phosphate insecticides have already been reported among people engaged in their manufacture.

An example of how these insecticides can make human food poisonous occurred in Singapore. One evening in September 1959 thirteen children and one adult were admitted to hospital. All were collapsed and many had fits ; those severely affected became deeply unconscious and four of the children died. Acting with commendable speed, the clinical staff suspected organo-phosphate poisoning and the public health authorities found that all the patients had consumed barley, recently imported from Europe. Early next morning they were able to issue administrative instructions making ‘ barley poisoning ’ notifiable. Prompt action limited the total number of cases to thirty-eight, with nine deaths. Subsequent analyses showed that the barley was contaminated by the agricultural insecticide, Parathion (*O*, *O*-diethyl *O*-*p*-nitrophenyl phosphorothionate). Kanagaratnam *et al.* (1960) have written a dramatic account of the outbreak and of the methods which enabled them to curtail it.

It is also necessary to keep in mind the possibility of chronic, long-term effects that are not immediately obvious.

CHEMICALS DELIBERATELY ADDED TO FOOD

Chemical substances are added deliberately to food, usually for specific and generally altruistic motives ; the chief of these are discussed below.

Prevention of infection and putrefaction

When private enterprise began seriously to tackle the problem of providing acceptable food for the townsman, chemical aids were naturally invoked. The industry developed rapidly at a time that coincided with the discovery of bacteria, so that interest was soon focused on keeping mass-distributed foods free from bacterial putrefaction, without too much regard for their nutritive value which was as yet barely understood. The easiest means was (and still remains) sterilisation by heat ; yet this may not only alter the flavour of some foods (in part by denaturing their proteins), but can also (as we now know) destroy heat-labile vitamins, especially ascorbic acid. Moreover, if foods are sterilised by boiling in water other nutrients are liable to be removed by solution. The first crude attempts to keep food free from bacteria by chemical means were not very successful ; milk was treated with formalin or borax with results that were not only distasteful but toxic. It became necessary to introduce legislation in Great Britain forbidding the addition of any chemicals to milk and advising instead pasteurisation. Nevertheless a number of mild bacteriocides such as benzoic and sulphurous acids were subsequently introduced and legally permitted, particularly for the preservation of canned and bottled foods. Several such bacteriocides have now been in use for years without any demonstrable harm to the consumer. Nevertheless the problem of ensuring that food is free from infection is never properly solved by the addition of chemical disinfectants. The first line of prevention should be insistent pressure by the distributor on the producer to sell him a clean product.

In recent years antibiotics have inevitably found their way into the field of food preservation. Aureomycin particularly has been introduced to protect such foods as chicken and fish from surface contamination: this postpones for several days the time when they cease to be acceptable to the purchaser, so that rapid (and expensive) transport is no longer needed to get them to the city shops. Traces of aureomycin are said to be destroyed in most cooking processes; if this is true there can be no objection to its use, provided that the amount employed is carefully controlled. But the indiscriminate introduction of antibiotics into foods —without the most careful attention to the nature of the antibiotic used and the dose in which it is employed—may well be dangerous. The use of penicillin or aureomycin applied locally to cows' teats to prevent or treat staphylococcal mastitis is another example. Already the medical profession is plagued by varieties of staphylococci that have become resistant to antibiotics through repeated exposure of patients to small and therapeutically inadequate doses. Furthermore, even traces of antibiotics, if regularly ingested, may completely alter the normal relationship between a man and the bacteria that live in his bowels. Clearly both doctors and dietitians must watch with anxiety the introduction of antibiotics into food technology.

Sterilisation of processed foods and inhibition of enzyme activity can be achieved by using ionizing radiation in dosages (one hundred thousand to one million rads) which are not dangerous to the consumer. Resulting changes in flavour, colour or texture and reduction in vitamin content of certain foods have so far prevented the commercial application of such methods.

Improvement of flavour

Chemicals are sometimes added to proprietary brands of food to make them more appetising. There is no harm in this practice so long as it is known for certain that the substance added is metabolised by the human body. For instance glutamic acid (obtained from wheat gluten) is a pure amino acid which the cells of the body normally utilise. Its strong, meaty flavour makes it a useful seasoning for soups and stews. Some wholesome foods are by nature insipid, tasteless or even slightly nauseating without some spice to enliven them. This need has been known from the earliest times and accounts for the cultivation of garlic in the Latin countries, of leeks in Great Britain and indeed for the ancient spice trade that maintained commercial relations between Europe and the Orient. It is most important, however, to be sure that all flavouring agents are safe; natural products should be preferred to synthetic chemicals with dubious pharmacological properties. Children's sweets (candy), flavoured with amyl acetate and called ' fruit drops,' should be discouraged. Of the synthetic sweetening agents, saccharine has been employed for over 70 years without apparent harmful effects ; it is a useful aid in the treatment of obesity and diabetes. But ' dulcin,' a sweetening agent formerly prescribed, has been found to have harmful effects on animals if administered over a long period, and so should be banned.

Improvement of appearance

American food producers often talk of ' eye appeal,' and certainly foods that look attractive sell well. No one can seriously quarrel with the practice of window-dressing so long as it is harmless. " Little dabs of lipstick, little daps of paint, make a plum's complexion look like what it ain't." The vanity of the food salesman can be as likeable as that of a fashionable lady. An orange with a clean bright skin is attractive, even though achieved by chemical treatment.

Use of dyes in food.—The use of dyes to disguise the true nature of a food involves more serious issues. The moralist may well question the ethics of dyeing kippered herrings brown so that they appear to have been kiln-cured when in fact they have not ; of dyeing cakes yellow, suggesting that they have been made with eggs, which is often not the case; or of dyeing vanilla-flavoured swiss roll brown, giving the misleading impression that it contains chocolate.

Nevertheless good colour certainly adds to the attractiveness of food and thus to better appetite. There is no valid objection to the ancient culinary art of using natural pigments such as burnt sugar (caramel) or cochineal to catch the customer's eye. Anxiety only begins when unnatural, synthetic dyes come to be used, and of these the ' coal-tar ' azo dyes, first discovered by German chemists, are potentially the most dangerous. Some of them have been shown to produce cancer in animals when administered over a long period. The difficulty is that it is impossible to predict, from the chemical formula of a synthetic dye, whether it is likely to be carcinogenic or harmless.

The British attitude towards justice has always been that a man is innocent until proved otherwise. This same attitude has been generally applied to the problem of chemical additives to food. Legislation has been slow to ban any particular practice of food manipulation until there is positive evidence that it is harmful. Such evidence was often clear in the early days, when arsenic or lead poisoning for instance created acute dangers which resulted in immediate public demand for administrative action. But the possible long-term effects of chemical additives are of little concern to the modern man in the street, who has sufficient other day-to-day problems to occupy his mind, and so continues to smoke cigarettes and to eat foods coloured with synthetic dyes, despite the warnings of the scientists.

It was thus a departure from the usual easy-going tolerance in Great Britain when the Foods Standards Committee appointed by the Minister of Food issued a report (Ministry of Food, 1954) advocating the exclusion of all dyes from food, except for a carefully selected list of colouring agents which, on present evidence, are thought to be harmless. In this the committee was following the principle adopted by the Foods and Drugs Administration of the U.S.A., and also by the Government of Canada, in publishing a list of *permitted* additives in place of a shorter list of *forbidden* substances whose crimes against health had been proved.

Improvement of texture and keeping qualities

The prime example of chemicals used for this purpose is to be found in the ' improvers ' employed by the milling industry. Nitrogen trichloride was introduced in the 1920's under the trade name ' agene ' for improving the ' strength ' of flour. In 1946 Sir Edward Mellanby proved that bread made from agenised flour, when fed to dogs, gave them fits, known popularly as ' running fits ' or ' canine hysteria.' The ' improver ' combined with parts of the protein in wheat to produce a substance highly toxic to dogs and several other species. Although there is no certain evidence that it is toxic for man, the use of nitrogen trichloride has been abandoned in British milling and is largely replaced by chlorine dioxide.

Other examples are the propionates added to flour to inhibit mould growth in bread ; emulsifiers such as those used to prevent separation of salad dressings ; anti-oxidants to keep fatty foods from becoming rancid ; and thickening agents.

Carcinogens in Food

In 1928 Sir Ernest Kennaway isolated dibenzanthracene—the first pure chemical substance shown to produce cancer in laboratory animals. His search was prompted by the high incidence of cancer of the scrotum and other parts of the skin among chimney-sweeps, cotton spinners and shale-oil workers who are constantly exposed to soot or oil. Tar and pitch were also found to be carcinogenic. From these materials a number of other cancer-producing chemicals have since been isolated. Many other unrelated chemical carcinogens have also been identified ; they include certain hydrocarbons, azo dyes and aromatic amines.

The question naturally arises, Are carcinogenic chemicals commonly present in human food ? No certain answer can as yet be given. Obviously they could be present as deliberate additives, as accidental contaminants or as natural ingredients of foodstuffs. There can be no dispute that certain substances deliberately added to food have subsequently been proved to be carcinogens. Examples are : the use of ' butter yellow '—an azo dye—which was used for colouring margarine until proved, in 1936, to be carcinogenic for laboratory animals ; the use of dulcin as an alternative sweetening agent to saccharin until it was found to cause liver tumours in animals (Mellanby, 1951). Carcinogenic dyes have also been used to colour sausages red and oranges yellow.

Arsenicals are being increasingly used in agriculture and so may contaminate foods. For generations medical textbooks have stated that arsenic is carcinogenic ; the evidence for this is slight. Nevertheless, arsenic must be added to the list of food contaminants which might be a possible cause of malignant disease. In addition, selenium, if added to the diets of rats in amounts from 5 to 10 parts per million, leads to the development of cancers after 18 to 24 months. The possible role of both arsenic and selenium as carcinogenic agents has been reviewed by Frost (1960). The evidence against them is negligible, except under highly artificial or extraordinary circumstances.

Since the advent of nuclear warfare, the risk of food becoming contaminated with radioactive materials, which may give rise to malignant disease, has considerably increased. This subject is discussed on page 359.

While there is as yet no proved case of cancer arising in man as a result of carcinogenic additives or contaminants in food—it is obviously a very difficult matter to prove—nevertheless the rising tide of cancer deaths in many civilised countries makes it highly desirable that every precaution should be taken to protect food from potential carcinogens, either deliberately added or accidentally introduced. Chemicals should not be added to food until there is ample evidence that they are harmless and not potential carcinogens in the amounts likely to be consumed.

Whether natural carcinogens exist in some human foods has been little investigated and must be a matter for speculation at the present time. The same is true of the many herbs used by man, though there is at least one initial warning ; herbs of the family *Senecio* are widely used by South African negroes either for medicine or magic. The European representative of this family is the common ragwort (*S. jacobæa L.*). Cook, Duffy and Schoental (1950) have shown that alkaloids extracted from ragwort are capable of inducing liver tumours in rats ; they speculate that the wide use of *Senecio* in Africa may contribute to the high incidence of primary liver tumour in that continent.

COMMENT

It should be evident from the brief outline given in the preceding pages that anyone living in a modern city inevitably ingests each day a variety of chemicals of whose presence he is unaware and whose pharmacological properties are little understood. A number of responsible people, both doctors and laymen, feel uneasy about this situation. The doctors know that urban patients suffer from a variety of degenerative and metabolic diseases that occur less commonly among simple rural peasants. Sir Edward Mellanby (1951), after pointing out that such diseases were often due to errors of living, went on to say : " It may be that one of these errors is the ingestion of food treated by unnatural chemical substances."

Clearly this is a potential menace to future health, the more so because the possible consequences are likely to be slow and insidious. Gone are the days of Dr Wakley's first crusade when an acute incident of chemical food poisoning could be investigated and solved by the local public analyst. It now needs a special kind of highly skilled biochemistry to detect many of the modern additives in the traces that may occur in food. Patient and elaborate laboratory research is needed to find out if they are harmful. The magnitude of this problem is well illustrated by the report in 1951 of the Delaney Committee appointed by the United States Senate. This committee found that out of 704 substances added to food in the U.S.A., 276 had not been established as harmless and therefore formed a potential public health problem. It would be useful in Great Britain to have a permanent committee, headed by a member of the medical profession, to keep the whole subject under review, to direct the research that is needed and—if necessary—to advise sanctions against any firms whose activities threaten the public health. The Food and Drug Administration in the U.S.A. has already shown the value of such work. The need for a strong committee of this kind in Great Britain has been repeatedly stressed by responsible people in recent years. It would seem unreasonable to expect the taxpayer to bear the whole cost of its activities ; as Sir Charles Dodds (1953) has said : " The onus of proving that a substance is harmless should properly rest on the shoulders of those who propose to use it." Perhaps the food industry would follow the lead given by the cigarette manufacturers and help to finance this official enquiry.

There are also international implications associated with the addition of chemicals to foodstuffs. A country like Great Britain that depends on food imported from abroad to supply a considerable part of its needs must rely on the foreign farmer to see that dangerous chemicals (often not easily detectable by a food analyst) do not contaminate food crops during their production. The experiences of food chemists from different countries should be shared, and this branch of scientific technology need not be hampered by national secrecy. It is therefore satisfactory to note that the Food and Agriculture Organisation of the United Nations and the World Health Organisation are making a special study of these problems. A joint FAO/WHO Expert Committee on Food Additives has produced a series of valuable reports, to which the reader is referred for more detailed information. These are entitled ' General Principles Governing the Use of Food Additives ' (FAO/WHO, 1957), ' Procedures for the Testing of International Food Additives to Establish their Safety in Use ' (FAO/WHO, 1958*a*), ' Evaluation of the Carcinogenic Hazards of Food Additives ' (FAO/WHO, 1961*a*), and ' Evaluation of the Toxicity of a Number of Antimicrobials and Anti-oxidants ' (FAO/WHO, 1962).

RADIOACTIVE MATERIAL IN FOOD

Food can become contaminated with radioactive material. This may be brought about by the testing of nuclear weapons and also by accidents at atomic power stations. This is a subject which has generated much emotion, but it has also led to careful and thorough investigation of the resulting hazards.

Ionizing radiations from any source have harmful effects on living tissues. The gonads are very susceptible and, if damaged, genetic effects may follow, leading either to sterility or to the production of offspring with a variety of malformations. Leukæmia and other types of malignant disease can arise as a result of irradiation. The life span of experimental animals has also been shown to be shortened.

Radiation hazards.—These are many and varied. Man is inevitably exposed to a variety of natural radiations. There are cosmic rays and radioactive material in the earth's crust. There are also many natural isotopes present, which are radioactive. All living tissues, including the human body, contain minute traces of carbon-14 and potassium-40. Recently man has become exposed to additional sources of radiation; these are from medical radiology, from television sets, from a variety of industrial processes, as well as from the 'fall-out' from nuclear tests. Table 24, 1, shows an estimate of the relative importance of these sources. It is impossible to state how much disease can be attributed to natural radiation inevitably present. It is equally impossible to state whether the recent additional exposure resulting from nuclear explosions has led to any increase in the incidence of leukæmia or malignant disease, or if it has caused or will cause any malformed infants to be born. The conclusion which might be drawn from an examination of Table 24, 1 is that at the time of writing the combined sources of radiation, including fall-out, give no cause for alarm in so far as the general population is concerned. However, there is justification for anxiety that an increase of radiation, particularly from the testing of nuclear weapons, might become a serious threat to health.

TABLE 24, 1. *The gonadal dose level of radiation in the United Kingdom* (*WHO*, 1962*a*)

Source	Annual dose rate in millirads
Natural background	85–106
Medical radiology, 1957 . . .	19
Miscellaneous sources (TV, X-ray, etc.) .	1
Occupational exposure, 1959 . . .	0·5
Fall-out (average value for 1955–1959) .	2·4

Fall-out consists of radioactive materials which are released as a cloud of dust at a great height consequent on the explosion of nuclear devices. The dust drifts in the stratosphere and the upper atmosphere and then settles slowly and is dispersed widely over the earth's surface. Most of it falls into the oceans. On land the distribution is uneven but is usually greatest in mountainous areas and in regions with high rainfall.

Vegetables, fruits and cereals can be directly contaminated. A more serious danger to man could arise from drinking milk and eating meat from cattle which had been feeding on contaminated herbage and had concentrated the radioactivity into their tissues and secretions. The most dangerous elements in the fall-out are strontium-90 (^{90}Sr, half life 28 years), cesium-137 (^{137}Cs, half life 30 years) and iodine-131 (^{131}I, half life 8 days). These isotopes are treated as biological material in the same metabolic manner as the inert elements. Strontium in general has properties similar to calcium and is concentrated in bone and in milk (p. 170) ; the physiology of iodine has been briefly discussed on page 186. Cesium is treated metabolically in a manner similar to potassium and accumulates in muscle and other soft tissue.

Iodine-131 disintegrates rapidly. The majority of the ^{131}I liberated by a nuclear explosion will become inactive in the upper atmosphere. In the first few weeks after nuclear tests it undoubtedly constitutes a hazard to health, and it may be a real danger in the immediate neighbourhood of atomic power stations after an accident, as happened at Windscale in the North of England in 1957.

The ^{131}I which falls on the pasture on which cattle are feeding is readily incorporated into their milk. Milk is the food which is most likely to act as a vehicle for a dangerous dose. The Medical Research Council (1961) have laid down that the ^{131}I content of milk should not exceed 130 micromicrocuries/*l.* on average over a year. This level has been chosen so as to provide a margin of safety against damage to the thyroid gland. (The micromicrocurie, $\mu\mu$C, is one thousandth of a millionth of a curie. The curie, the basic unit of disintegration, is the disintegration of one gram of radium-226.) The Agricultural Research Council Radiobiological Laboratory examines systematically the milk from many parts of the United Kingdom. After the resumption of nuclear tests in September 1961 the mean content of ^{131}I during the following two months was as follows :—

Week commencing	$\mu\mu$C ^{131}I per litre of milk
September 16	85
September 24	109
October 1	138
October 8	150
October 15	114
October 22	158
October 29	127
November 4	117

These average figures cover wide local variations and in parts of Wales, Scotland and Northern Ireland values considerably above 160 have been found.

As already explained, because of its short life the dangers from a single source of ^{131}I are short lived. With adequate sampling and the provision of a sufficient reserve of dried or tinned milk, the danger can be averted by prohibiting the consumption of milk from cows grazing on affected pastures. The prohibition would not be expected to last for more than a few weeks. Up to 1962 the level of contamination of the milk in any area has not risen sufficiently high for a long enough period to cause, in the opinion of competent authorities, any risk to the thyroid gland.

Strontium-90 is probably the most important source of radioactive contamination of food from nuclear explosions. This is on account of its long half life of 28 years and the fact that it is mainly concentrated and stored in the bones. Such stored ^{90}Sr can damage bone marrow and other tissues over many years.

It has been estimated that the mean daily intake per head of ^{90}Sr in the United Kingdom in 1958 was 6·65 $\mu\mu$C/day (Hawthorn, 1959). Over half of this was present in milk. The amount present in vegetable foods is very variable and a significant amount of this can be removed by washing and discarding the outer leaves and skin.

Owing to its close association with calcium, the amount of ^{90}Sr present in foods or tissues is often expressed on a basis of their calcium content. One strontium unit (SU) represents 1 $\mu\mu$C ^{90}Sr/g. Ca. This is the most satisfactory way to evaluate the radioactivity of strontium in a diet. Due to the high calcium content of milk and the exceptional importance of milk in the diets of children, its degree of radioactivity has been carefully investigated for a number of years. The concentration of strontium-90 in the milk supplies of the northern hemispheres has increased as more and more nuclear fall-out returns to the earth's soil and vegetation. Values have varied from 2 to 16 strontium units (SU). Vegetables and cereals may contribute much more radioactive strontium to an adult's diet than does milk. A good example of the contribution which contaminated vegetables can make to the radioactivity of diets and one which is unrelated to fall-out, was provided recently in an area of the United States near a uranium refinery ; milk contained only 5 SU, whereas the range in potatoes was 37 to 50 SU, in cabbage 210 to 682 SU and in lettuce 86 to 4420 SU.

Average daily diets in the northern hemisphere were found to supply between 6 and 8 SU per day in 1958. Fortunately only a fraction of this amount is absorbed and hence reaches the tissues, and the accumulated concentration of radioactivity in human tissues is not yet believed to be a serious hazard to health. The resumption of atmospheric nuclear testing in 1961 may well alter this state of affairs, with results which are unpredictable from the present state of our knowledge of the long-term clinical effects of exposure to low levels of radiation.

The amount of ^{90}Sr that can accumulate in bone without causing an appreciable increase in the risk of leukæmia and bone tumours cannot be stated with confidence. An International Commission on Radiological Protection (1960) has suggested that the risk is negligible unless the ^{90}Sr level in bone is over 67 SU. In young children in Britain in 1961 the average level was about 4 SU. This is much more than is present in adults, whose bones were formed before there was any fall-out. There will almost certainly be a further rise in the next few years, but unless there is a great increase in fall-out, this is not likely to reach dangerous levels.

Cesium-137 presents a hazard which is difficult to assess. It has a long half life and is readily absorbed and concentrated in muscles. Thus the meat from animals grazing on contamimated pasture might become dangerous. ^{137}Cs appears to have been studied much less than ^{131}I and ^{90}Sr.

Protection from dietary radioactivity

The capacity of man and cattle to discriminate between calcium and strontium during the processes of absorbing and excreting these elements provides a measure of protection to populations accustomed to obtain a considerable proportion of their food from animal sources. However, the content of radioactive strontium in vegetable foodstuffs contaminated by fall-out or other sources is a potential hazard which applies to all mankind, particularly to those people accustomed by environmental necessity to eat diets mainly composed of cereals and vegetables.

Larsen (1960) demonstrated that increasing the consumption of uncontaminated calcium reduces the absorption of radioactive strontium. If the political stupidity of man ever makes it necessary to use such uncontaminated calcium to reduce the rate of accumulation of radioactivity in his tissues, it should be obtained from mineral deposits deep in the earth.

It has long been known that lactose and other higher sugars facilitate the absorption of calcium. Thus milk itself, if uncontaminated, could be of value for reducing the accumulation of radioactivity in the body. Methods for the removal of radioactive materials from milk are being developed, but the current cost of such operations, if they were to be used on a commercial scale, is estimated to be approximately 6d. per pint.

Foods which can be packaged and stored can be protected quite easily against fall-out. Complete protection can be achieved by the use of air-tight tin cans or jars, which are preferable to single-layer wrappers of paper, cellophane or polythene which may not be sealed satisfactorily and are not always impervious. If the outside of such containers is known to have been contaminated they should be washed thoroughly with uncontaminated water before opening. Most fruits which have a protective skin, such as oranges or bananas, can be eaten with safety provided they are well washed before peeling. It has been demonstrated that induced radioactivity is not set up in tinned foods which have been exposed to the intense radiation encountered near the centre of nuclear blasts.

National and international action

A close watch is being kept by governments and international agencies on the extent to which foodstuffs are becoming contaminated by fall-out and in the vicinity of atomic plants. In Great Britain the milk supply is analysed every two weeks for radioactive strontium, iodine and cesium, as well as for stable calcium and potassium. Up-to-date accounts of the radioactivity of foods in Britain can be found in reports of the Agricultural Research Council's Radiobiology Laboratory. These are published once or twice a year and are obtainable from H.M. Stationery Offices. In the United States, the Atomic Energy Commission, the National Academy of Sciences and the Public Health Service publish periodic summary reports.

The United Nations Scientific Committee on the Effects of Atomic Radiation collates information which originates from member governments and from the International Atomic Energy Agency, the Food and Agriculture Organisation and the World Health Organisation.

Conclusion

We must be on our guard against undue panic on the one hand and undue complacency on the other. We can, however, express our indignation and disgust that the political leaders of the great nations are unwilling or unable to agree to the immediate cessation of atomic explosions and to take the necessary measures to ban for ever the use of nuclear weapons as a means of settling international disputes.

CHAPTER 25

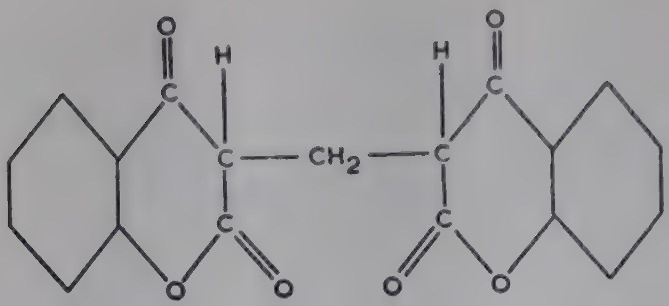
FOOD POISONS: (3) NATURAL POISONS

BEFORE the advent of the synthetic drug industry early in this century, most of the pharmacopœial drugs originally came from herbs collected in the countryside. All drugs are toxic if taken in excessive doses, and many common plants are potentially poisonous, if eaten in large amounts. Most country-born children have a practical knowledge of local poisons, but occasionally errors are made. In Great Britain perhaps the most common is the eating of the fly toadstool (*Amanita muscaria*). This contains muscarine, but only in small amounts. The characteristic symptom of poisoning is cerebral excitement, which is due to mycetoatropine (Ramsbottom, 1953). Far more dangerous is the Death Cap toadstool (*Amanita phalloides*). This is not easily distinguished from the edible field mushroom, *Agaricus camprestis*. Elliott *et al.* (1961) describe a severe attack of poisoning and also give notes on the identification of poisonous fungi. Their patient, a farmer who had eaten *Amanita phalloides* in error, was acutely ill when admitted to Cumberland Infirmary under Dr Rolland. He became unconscious, had watery diarrhœa and was jaundiced. After 48 hours his urine was suppressed, but he finally recovered after extracorporeal hæmodialysis (artificial kidney). Children on blackberrying expeditions occasionally eat the fruit of the deadly nightshade (*Atropa belladonna*); a rapid pulse, cerebral confusion with restlessness and a hot dry skin provide evidence of acute atropine poisoning. Common garden shrubs or trees may also be toxic. In Edinburgh, children who eat the seeds of the common yellow laburnum (*Laburnum vulgare*) are occasionally poisoned by the alkaloid they contain (Mitchell, 1951).

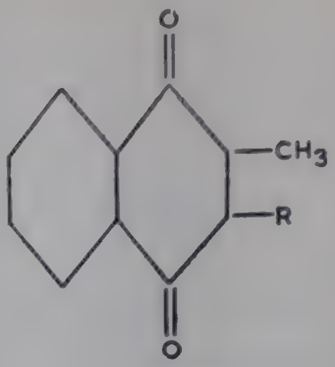
Antivitamins

Recently a new class of poisons has been discovered—the antivitamins. Attention was first drawn to these substances in veterinary practice. Cattle fed on spoiled sweet clover develop a hæmorrhagic disease. This is due to the presence in the clover of dicoumarin, a substance chemically related to vitamin K (Link, 1944). It produces hæmorrhages by causing vitamin K deficiency in the tissues. Apparently the dicoumarin molecule gets attached to an enzyme system in the place where a molecule of vitamin K should be, thus blocking the action of the vitamin. Dicoumarin derivatives are now widely used in medicine to prevent thrombosis. Several other diseases attributable to antivitamins are known in veterinary practice and one, Haff disease (p. 369), in human medicine.

Chemists have prepared many substances, with chemical structures



dicoumarin



vitamin K

similar to the well-known vitamins, which act as antivitamins, presumably by blocking the enzymic site of the action of the vitamin. Some of these, besides dicoumarin and its derivatives, may be of value in medicine. Antifolic acids can inhibit the growth of malignant tissues. They can slow the downhill course of acute leukæmia. It is possible that antivitamins may in the future be of practical value in the treatment of cancer, but so far, results have been disappointing.

A healthy person living on an ample mixed diet has usually no difficulty in dealing with small amounts of most natural poisons. The enzymes necessary to destroy them may be present in the digestive tract, liver or tissues. Alternatively, the poisons may be excreted in the urine or through the gut. Except when the metabolic defences of the body are impaired by previous malnutrition, moderate doses of these natural food poisons are not an important matter. Examples will now be given of several reputable foods which may, under certain circumstances, be poisonous.

Maize

The impoverished maize-eater often develops pellagra (Chapter 34). The principal signs and symptoms of this disease are readily cured by nicotinic acid and there can be no doubt that nicotinic acid deficiency is the principal cause. But it is not the only one and the epidemiology of pellagra cannot be explained solely by the lack of nicotinic acid (Aykroyd & Swaminathan, 1940). It has been shown that maize bran contains a toxin which retards the growth of rats (Kodicek *et al.*, 1947 ; Borrow *et al.* 1948). This toxin has not been identified chemically and naturally there is reluctance to interpret experimental results on rats as applying directly to man.

Rye

When rye was widely cultivated in Europe, outbreaks of a disease known as ‘ St Anthony’s Fire ’ or ergotism were not uncommon. In the Middle Ages sufferers made pilgrimages to St Anthony’s shrine. It is now known that rye is liable to infection with ergot, a rust which contains a number of toxic alkaloids. Barger (1931), who with Sir Henry Dale elucidated their chemical nature and pharmacological action, describes in his book both the properties of the alkaloids and the history of the epidemics. Sir Edward Mellanby (1934) pointed out that outbreaks of ergotism have usually been associated with times of food scarcity. Deficiency of vitamin A and other factors may well contribute. Outbreaks of ergotism are still occasionally reported from Eastern Europe, where rye is eaten. Again it must be emphasised that rye is a wholesome food. Poisoning results from its consumption only when the grain is infected by rust.

Tares (Vetches)

Tares is the traditional English name for the vetches, which are pulses allied to the peas and beans. In Biblical times they were poorly regarded. " But while men slept, his enemy came and sowed tares among the wheat " (St Matthew, xiii. 25). Why the sowing of tares was regarded as an unfriendly act is not wholly clear. The tendrils by which these plants climb up the wheat stalks certainly hamper reaping. But they may also have been known to be nutritionally unsatisfactory.

More recently one species of tare (*Lathyrus sativus : Khesari dhal* in Hindustani) has been deliberately sown with the wheat by farmers in India and the Middle East, as a drought-resistant crop. The seeds are commonly sown mixed with wheat. If the rains are good the wheat overgrows the lathyrus—of which little is harvested. If the rains fail and there is a poor crop of wheat, a useful harvest of lathyrus may be reaped. Eaten in small quantities, lathyrus seeds are a useful and valuable food. But if they are the main source of calories (providing more than 50 per cent.), a severe disease of the spinal cord (lathyrism, p. 448) may result, causing crippling and permanent paralysis. An excellent account of the disease and the circumstances under which it arises has been given by a soldier, General Sleeman (1844). The exact nature of the toxin in the seeds, responsible for the disease, is still unknown. Laboratory animals seldom, if ever, suffer from eating *Lathyrus sativus* and this has handicapped research. Allied vetches, notably the sweet pea, when fed to rats (Ponseti, 1954), readily give rise to a disease which, however, is unlike human lathyrism ; there is a marked disturbance of collagenous structures throughout the body, notably in skin and bones. The bones become weak, but the nervous system is usually spared. In the arid regions of North America, horses and cattle sometimes suffer from a neurological disease called ' loco,' attributed to eating a particular species of pulse. Perhaps all vetches contain potential toxins ; we may not have heard the last of this class of plant either in human or veterinary medicine.

There is a further possible explanation of the Biblical suspicion of ' tares.' The seeds of another plant—*Lolium temulatum* (which is not a pulse)—commonly get mixed with wheat grown in Abyssinia and Aden. These seeds when ingested produce a condition resembling alcoholic intoxication (Brinton, 1946). The local name for this weed is *miscara*, and in English ' flax darnel.'

Mustard oil

In Bengal and Behar mustard oil is the chief cooking fat. In the same part of the world epidemic dropsy has been endemic for a long time. In a series of investigations in which the clues were analysed in the best detective manner, Lal and his colleagues (1937, 1940) showed that mustard oil was responsible for this disease. The toxin was not present in the oil from the mustard seeds themselves, but in oil from the seeds of a poppy weed (*Argemone mexicana*). This weed commonly grows in the mustard crops. The seeds of this weed have been shown by Sarkar (1948) to contain an alkaloid, sanguinarine, which is toxic. Sanguinarine inhibits the oxidation of pyruvic acid and, as in wet beriberi, pyruvic acid may accumulate in the blood of patients suffering from epidemic dropsy (Wilson & Ghosh, 1937).

Seawater fish

There are a number of species of fish found in certain tropical and subtropical seas, especially in the Pacific Ocean and the Caribbean Sea. Some of these are always poisonous and others may usually be eaten with safety and yet are poisonous at certain times of the year. This type of poisoning must not be confused with that due to eating fish contaminated with food poisoning organisms. It must also be distinguished from the poisoning which results when a person is wounded by a venomous fish which carries a poison apparatus. Venomous fish have a world-wide distribution. Poisonous fish have usually been feeding on a coral reef, and deep sea fish are generally safe. The barracuda is one of the exceptions to this rule. The poison is almost certainly manufactured by single-celled Dinoflagellates, particularly *Gonyaulax catenella*. Small crustacea feed on these and larger fish on the crustacea. The toxin is stable and remains in the tissues of fish, which do not consume a lethal dose. It is not destroyed by cooking. The chemical nature of the toxin is not known, but like the toxin of botulism very small doses may be lethal to man. It probably acts by interfering with humoral transmissions of nerve impulses by acetylcholine.

Dinoflagellates at times multiply to such an extent that they may colour the water and this may explain one of the plagues of Egypt. ‘ All the waters that were in the river were turned to blood and the fish that were in the river died ; and the river stank, and the Egyptians could not drink of the water of the river ’ (Exodus 7, 20, 21). Very little is known about the factors which determine the sudden increase in numbers of these flagellates (Hutner & McLaughlin, 1958).

However, the clinical features of the poisoning are well known. Captain Cook (1777) was familiar with them as the following passage shows :—

5the September, 1774, Cape Colnet, New Caledonia. “ This afternoon a fish being struck by one of the natives near the watering-place, my clerk purchased it, and sent it to me after my return on board. It was of a new species, something like a sunfish with a large, long, ugly head. Having no suspicion of its being of a poisonous nature, we ordered it to be dressed for supper: but, very luckily, the operation of drawing and describing took up so much time that it was too late, so that only the liver and row were dressed, of which the two Mr Forsters and myself did but taste. About three o'clock in the morning we found ourselves seized with an extraordinary weakness and numbness all over our limbs. I had almost lost the sense of feeling; nor could I distinguish between light and heavy bodies, of such as I had strength to move; a quart pot full of water and a feather being the same in my hand. We each of us took an emetic, and after that a sweat, which gave us much relief. In the morning, one of the pigs which had eaten the entrails was found dead. When the natives came on board and saw the fish hang up, they immediately gave us to understand it was not wholesome food."

The muscular weakness and changes in sensation described above are characteristic; the tendon jerks are often absent. Itching may be very severe. Pain, especially in the muscles and bones of the neck and back, is usually present at the start. The attack is most frequently of moderate severity and muscle power returns after a few days. The itching may persist for weeks. Occasionally there may be widespread paralysis and coma, and death may ensue. Treatment does not appear to have progressed further than the traditional use of purgatives and emetics and symptomatic remedies for pain and itching. Further information about poisoning by tropical fish may be found in an interesting paper by Dr Raymond Mills (1956) who has himself suffered from poisoning in the New Hebrides.

Occasionally in America (Meyer, 1953) and very rarely in Scotland and other parts of Northern Europe (Gemmil & Manderson, 1960) shellfish have been responsible for poisoning with neurotoxic symptoms similar to those described above.

Freshwater fish

In 1936 an outbreak of paralysis developed in silver foxes on a farm in the U.S.A. The foxes had been fed on carp. The presence of an antithiamine was demonstrated in the flesh and viscera of these fish (Green *et al.*, 1942). Additional thiamine both prevented and cured the disease. In Sweden (Berlin, 1948) a similar condition occurs in man, known as Haff disease. It arises from the consumption of various freshwater fish—pike, perch, bream, roach, eel and burbot. There is an acute inflammatory reaction in the muscles. The cause is thought to be an antivitamin in the flesh of the fish, which inactivates thiamine. Yet the varieties of fish that are implicated are eaten in other regions or in other countries with impunity. The cause of the poisoning may be related to the quantity eaten, the lack of sufficient cooking (which destroys the antivitamin) and the previous state of nutrition of the consumer in respect of thiamine (perhaps including the use of alcohol).

Ackee fruit (*Blighia sapida*)

This grows profusely in Jamaica. The fruit is eaten by large numbers of people, especially children. Yet it is widely credited with being responsible for a form of food poisoning, ' vomiting sickness ' (Hill, 1952 ; Jelliffe & Stuart, 1954). Dr Cicely Williams (1954*a*) undertook an investigation of the disease for the Jamaican Government. She was able to study numerous patients and a few outbreaks in detail. In some, the symptoms could be attributed to diseases such as meningitis, heavy ascaris infestation and dysentery. Other outbreaks might reasonably have been attributed to staphylococcal food poisoning. Yet there were several patients in whom no definite cause could be found, despite thorough investigation. A specific poison from the ackee fruit could not definitely be excluded. She concluded that if such a poison were indeed responsible, large amounts would have to be consumed, and the patients must be peculiarly susceptible to the poison, probably because of their poor state of nutrition. Her report confirms previous statements that ' vomiting sickness ' rarely occurs except in children who are gravely undernourished. On the charge of causing ' vomiting sickness,' the ackee fruit must be dismissed with the Scottish verdict ' not proven,' until more evidence accumulates.

Cabbage

It is easy to produce enlargement of the thyroid gland in rabbits by feeding them with large quantities of cabbage or other members of the Brassica family. Brassicæ possess sulphur-containing compounds, which may inhibit the formation of the thyroid secretions. However, there is no evidence that cabbage, as part of a well-balanced human diet, is anything but beneficial. The causes of goitre are complicated, and further discussed in Chapter 55.

Toxins produced by moulds

In 1960 a widespread outbreak of a fatal disease characterised by acute enteritis and hepatitis occurred in England among young turkeys which had been fed a ration containing imported groundnut meal (Sargeant *et al.*, 1961 ; Lancaster *et al.*, 1961). The groundnuts concerned had been harvested, stored and processed under conditions of high humidity. It was found that the toxic factor, as yet unidentified, was produced by *Aspergillus flavus*, a mould contaminating the nuts. The toxin concentrated from the infected groundnut meal was also found to be lethal to ducklings in very small quantities.

It has been known for some years that cattle fed on poorly stored damp maize often develop a similar disease if the grain is infected by *A. flavus*, and that the toxin is secreted in cow's milk. No harmful results from eating foodstuffs contaminated with this mould have yet been observed in man. The nature of the toxin and its effects when fed to rats and other animal species are being investigated.

COMMENT

In this chapter we have given a brief account of some of the natural food poisons and references to the literature on them. There is no reason to conclude that the list is complete. In any rural district where an obscure malady arises or already exists, it is always proper to consider the possibility of a natural food poison. Only two or three natural antivitamins have so far been discovered and identified. There may well be others, and some may contribute to human illness. The biological significance of these and other natural poisons is an interesting field for speculation.

PART III—PRIMARY NUTRITIONAL DISEASES

CHAPTER 26

SUBNUTRITION AND STARVATION

SUBNUTRITION and starvation arise (1) when there is not enough food to eat, for instance in times of famine, (2) when there is severe disease of the digestive tract, preventing the absorption of nutrients, as in the malabsorption syndrome and cancer of the œsophagus or (3) when there is a toxæmia which prevents the normal metabolism of the nutrients by the tissues ; such a toxæmia might be metabolic in origin (*i.e.* in renal or hepatic failure) or due to severe and long-continued infection. In all these circumstances there is wasting of the body with much loss of both muscle and fat. This gives rise to a clinical picture with an underlying morbid anatomy and chemical pathology which is essentially similar whatever the primary cause.

Historically there have been three distinct phases in the scientific investigation of subnutrition and starvation during this century. In the period before the First World War there were several professional fasting men. These strange creatures were prepared to go for periods up to 30 days without food. They were much studied by physiologists and from these experiments valuable information was obtained, especially in regard to the importance of endogenous protein metabolism ; this was ably summarised by Lusk (1928) in successive editions of his classic book. Between the two wars the subject attracted little attention ; in this period vitamins dominated nutritional research. The Second World War brought about widespread subnutrition and starvation in many parts of the world. They became matters of practical importance to many doctors. Five excellent monographs are available. Smith and Woodruff (1951) and Helweg-Larsen *et al.* (1952) describe their own experiences in Japanese and Nazi prison camps ; Burger *et al.* (1948) report on starvation in Holland during the winter of 1944-45, and the workers in the Department of Experimental Medicine, Cambridge (1951) give an account of the undernutrition in Germany in the immediate post-war years. Keys *et al.* (1950) describe a laboratory experiment in which 32 young men volunteered to live for 6 months on a diet providing only 1600 Cal./day. As a result they became severely undernourished, losing about 25 per cent. of their body weight.

Since the end of the Second World War mankind has been fortunately free from major famines and nutritional disasters. There has, however, been a great interest taken by physicians and surgeons as well as by laboratory workers in the study of the subnutrition that arises secondary to disease. Much new knowledge has been gained, especially in relation to chemical pathology and methods of treatment. Significantly the most important recent book dealing with this subject is written by a surgeon (Moore, 1959).

This chapter is concerned primarily with the clinical features, pathology and treatment of starvation. Other relevant material will be found elsewhere, *e.g.* the effects of diseases of the digestive tract (Chapter 38), special feeding methods (Chapter 48), the numerous causes of a failure in food supply (Chapter 49) and some administrative measures in famine relief (Chapter 53).

Morbid anatomy

Wasting of the tissues is the most characteristic feature of starvation. At autopsy a patient who has died of starvation may have little or no remaining adipose tissue. As a result the skin is loose. There is also marked atrophy of the skeletal muscles. Superficial œdema is usually present ; its distribution is largely determined by gravity. Fluid may also be found in the peritoneal and pleural cavities.

There is also atrophy of all the viscera except the brain, which is always spared. Atrophy of the heart is marked. In an adult man in health, the heart weighs about 350 g. Porter (1889) who performed 459 autopsies on victims of an Indian famine found that in 45 per cent. of the men the heart weighed less than 170 g. and in some cases no more than 100 g. This atrophy, if severe, is often irreversible and the subsequent failure of the circulation is a frequent cause of death. Atrophy of the small intestine, which affects both the mucous membrane and the muscular walls, is always present and may be very severe. Donovan (1848) writing of his experiences in the great Irish famine states that he observed " total disappearance of the omentum, and a peculiarly thin condition of the small intestines which (in such cases) were so transparent that if the deceased had taken any food immediately before death, the contents could be seen through the coats of the bowel." In 1945 one of us (S.D.) saw a similar picture in persons dying of starvation in Belsen concentration camps. The virtual loss of the power to absorb nutrients by the atrophied intestinal mucous membrane greatly prejudices the chances of recovery.

Jackson (1925) has written an excellent monograph reviewing much past literature on the effect of starvation on the organs of man and experimental animals.

Adaptive changes

The wasting and loss of weight are at first rapid if food supplies are suddenly reduced, but gradually slow down even though there is no increase in the amount of food eaten. There are four reasons for this slowing down :—

1. With the wasting of the body, the ' lean cell mass ' (p. 4) of

actively metabolising tissue is reduced and therefore requires less energy to maintain its vital activities.

2. The metabolism of the remaining tissues is reduced in intensity.
3. The body, being lighter, requires less mechanical work to move it about.
4. All unnecessary voluntary movements are curtailed.

In these ways the body is able to achieve an important degree of biological adaptation to a restricted food supply. Indeed were it not for this adaptability, the human species might well have become extinct long since.

Twenty-five per cent. of the weight of a healthy, non-obese body can usually be lost without immediate danger to life. With greater losses the hold on life is very slender, but some have survived losses up to 50 per cent. of their initial weight.

Changes in body composition in starvation

The wasting of tissues during starvation greatly affects the chemical composition of the body. Table 1, 1 (p. 1) sets out the chemical composition of the body of a normal man. In Table 26, 1 the alterations which may occur after he has lost 25 per cent. of his original weight are given. The most obvious change is the disappearance of over 70 per cent. of the body fat. Another striking feature of the response to starvation is the constancy of the extracellular fluid, the volume of which remains virtually unchanged. In the starving person the extracellular fluid forms a much higher proportion of the total body weight (in the example it has risen from 23·1 to 30·7 per cent.). As a result famine œdema appears and this

TABLE 26, 1. *The changes in body composition of a man who in health weighed* 65 *kg. and then lost* 25 *per cent. of this weight as a result of starvation*

	In health	After starvation
	(kg.)	(kg.)
Protein	11	8
Fat	9	2·5
Carbohydrate	0·5	0·3
Water :		
Extracellular	15	15
Intracellular	25	19
Minerals	4·5	4·0
	65·0	48·8

These figures illustrate what may occur to the hypothetical normal man described in Chapter 1 as a result of starvation. For actual measurements of the changes in body composition after starvation the reader is referred to Keys *et al.* (1950) and Moore (1959).

is a constant and characteristic feature of starvation. The cells of the muscles and all the other tissues (except the brain) also shrink and there may be a loss of about 3 kg. of cell protein and 6 kg. of intracellular water (Table 26, 1). There is little carbohydrate in the body in health and so the loss on starvation can only be small. Unless the period of partial starvation has been very long, *i.e.* many months or even years, there will be little loss of minerals from the skeleton.

Associated with the constancy of the extracellular fluid volume there will be little change in the amount of sodium in the body, which may even be slightly increased. The total exchangeable sodium may be 2000 mEq. which is within the normal range (p. 142). With the shrinkage of the cells there is a marked reduction in the intracellular potassium, and the total exchangeable potassium may be as low as 2000 mEq. ; more than a third of the normal amount of about 3500 mEq. may be lost.

Stores of energy and survival

From a study of Table 26, 1 it can be seen that a normal man may lose about 3 kg. of protein, 6·5 kg. of fat and 200 g. of carbohydrate. These amounts of protein, fat and carbohydrate represent a reserve or store of just under 75,000 Cal. It must be emphasised again that these figures apply to a normal man. In an obese subject the reserve will be much greater and in a small thin person much less. If the normal healthy man is deprived of all food, but not required to take any exercise, energy expenditure will approximate to the basal rate, *i.e.* about 1600 Cal./day. At that rate of exhaustion the reserve will last for 45 to 50 days.

It will thus take a considerable time for a man to die of starvation. Many healthy people have taken no food for 14 days. The experience is unpleasant, but involves no serious impairment of physiological function and leaves no permament effect on health.

It will have been noted in Table 26, 1 that the reserves of carbohydrate are very small and do not provide sufficient calories to meet energy needs even for a day. Wherever possible it is desirable to provide a starving man with at least 100 g. of carbohydrate daily. This will prevent the onset of ketosis and also reduce the breakdown of endogenous protein to a minimum. There is experimental evidence that the brain can only utilise carbohydrate and not protein and fat. The oxygen consumption of the human brain is about 45 ml./min. This involves the combustion of 80 to 90 g. of glucose in the day. During complete starvation most of this must come from the conversion of protein to carbohydrate. Pawan (1959) has produced convincing evidence that all of the carbohydrate necessary for the brain cannot always be provided by protein and some conversion of fat to carbohydrate must take place. Biochemists still continue to deny this possibility. There can be no doubt of the therapeutic value of supplying carbohydrate to a starving patient.

Of the 75,000 reserve calories in the example quoted above about 17 per cent. will be provided by endogenous protein. This corresponds to the breakdown of 66 g. of protein daily, an amount which may be metabolised by a healthy non-starving person. Some people, during starvation, are able to reduce nitrogenous metabolism below this level and so conserve their protein reserves more effectively.

Disturbances of water balance

As already stated, when the tissues become wasted, the amount of extracellular water in the body is not correspondingly reduced, so that a relative excess of water accumulates, producing ultimately famine œdema. The mechanisms producing this water retention are not fully understood. They are certainly not simple, but the following factors may contribute.

1. **Level of plasma proteins.**—In famine conditions there is often a great shortage of dietary protein, leading to a lowering of the level of plasma albumin. The consequent reduction in the osmotic pressure of the blood contributes to the œdema. This is in conformity with the classical hypothesis of Starling, according to which the plasma proteins have a dominant role in controlling the passage of water from the capillary blood into the tissue spaces. There are, however, numerous records of famine œdema occurring in patients whose plasma proteins were within normal limits so that hypoproteinæmia can be only a contributory factor.

2. **Fall in tissue tension.**—Youmans (1936) was apparently the first to suggest that famine œdema may be due to a fall in tissue tension. When fat is lost and the tissues shrink, the skin is not sufficiently elastic to contract down to the new body size. In consequence there may be a fall in interstitial tension, leading to seepage of water from the blood into the tissues. The body may be said to become too small for its skin. Skin elasticity declines with age and this may explain why famine œdema is commoner in older people than in the young.

3. **Renal disturbance.**—Another factor that may be involved is a disturbance of the normal hormonal mechanisms regulating the excretion of water and sodium from the body. An early symptom of famine œdema is increased urine flow at night. This suggests that when the body stands upright, the normal renal excretion of water is impaired ; yet there is no demonstrable defect in the function of the kidneys in patients with famine œdema. Nevertheless in other gross metabolic disorders, notably cirrhosis of the liver, there is evidence that there may be an upset in the balance of hormones regulating water excretion, with a relative excess of the pituitary antidiuretic hormone. Whether or not there is a corresponding increase in aldosterone secretion leading to sodium retention in primary starvation is uncertain. Such an increase has been reported in post-operative patients (Zimmermann *et al.*, 1956). Famine œdema may thus be partly due to the hormonal failures discussed in the next paragraph.

Failure of hormone and enzyme production.—Many of the hormones and all the body's enzymes are complex proteins. It is not surprising, therefore, that when the starving body has been drawing on its tissue proteins for long periods as a means of maintaining the blood sugar there may be insufficient essential amino acids left for the normal synthesis of essential hormones and enzymes. Evidence of hormonal failure is not lacking in starvation. Amenorrhœa and delayed puberty are common features of starvation in women and girls. Men lose their libido and may become impotent ; they may develop enlargement of the breasts (gynæcomastia). In children there is often a growth of lanugo hair, especially over the forearms and back, as may be seen in other gross endocrine disorders. At least one of the explanations of the diarrhœa which is so often the terminal event in starvation is a failure in the production of digestive enzymes. Another enzyme—cholinesterase—normally present in the blood, is reduced in starvation and may provide a measure of the extent of subnutrition.

Clinical features

Plate XIII shows starvation in a Nazi concentration camp and in the Belgian Congo. The patients are thin and the lax skinfolds give evidence of recent loss of weight. The hair is dull, dry and 'staring.' The eyes are dull and sunken, yet wasting of the orbital tissues may make them appear unduly prominent, particularly since the scleræ are unusually avascular. The skin is thin, dry, inelastic ; often there is peripheral cyanosis, even in warm weather. Dirty brown splotches of pigmentation may appear over the face and trunk ; these were recognised during the last century as one of the stigmata of famine.

Polyuria at night is a frequent and troublesome symptom of impending famine œdema. When œdema begins to appear it is usually first noticed in the face if the patient is lying down, giving the patient a puffy appearance which may falsely suggest adequate nutrition. When the patient gets up and walks about, the fluid gravitates to the legs, causing at first ankle œdema, subsequently extending upwards.

The blood pressure is low ; the diastolic pressure may be impossible to estimate, while the systolic pressure may be as low as 70 mm. Hg. The pulse rate usually falls progressively during prolonged partial starvation. In severe cases it is often below 40/min. When wasting becomes marked the heart appears small on radiological examination.

Although a mild anæmia (Hb 9–12 g./100 ml.) is common, severe anæmia is not a feature of starvation. If found, it is an indication of other coexistent disease. Associated vitamin deficiencies seldom give rise to clinical signs in starving people ; it may well be that the need for vitamins is greatly reduced when the total metabolism of the body is lowered by starvation.

Loss of sexual function may be the first complaint, and amenorrhœa is common. Nevertheless conception may occur and pregnancy proceed to full term.

Symptoms related to the psychological state of starving people are of practical importance. Although the intellect is usually clear, the personality may be seriously deranged. The mind is never fixed for long on a single problem, except the desire for food. Mental restlessness is combined with physical apathy. The patient becomes self-centred and indifferent to the troubles of others, even those of his dearest friends and relatives. He worries and becomes hypochondriacal, even hysterical, about his own disability. He is extremely sensitive to noise and other petty irritations which may make him quarrelsome. These symptoms may intensify rather than diminish in the early stages of treatment; consequently the starving patient is difficult to manage. This feature of the disorder should be remembered and treated objectively by people engaged in famine relief, otherwise they may lose sympathy with those whom they are trying to help. They must never expect thanks for their kindness. Even in the last minutes of life, the patient dying of starvation may give a clear history of himself, though his account may be coloured by pathological emotion. In the last stages of starvation, the personality may disintegrate completely. A mother will steal from her child. Donovan (1848) described in elegant language the horrible results of breakdowns in family ties which occurred in a small town during the great Irish famine. Cannibalism has been reported in many countries of the world (including Scotland) in times of famine.

Starving patients may suffer from a variety of infections—malaria, cholera, typhus, relapsing fever, smallpox, tuberculosis—to name only a few. Tuberculosis may add to the clinical signs present, often in unusual ways, for infection in starvation may give rise to little or no fever.

CANCRUM ORIS.—This consists essentially of infective gangrene of the mouth, involving and eroding the lips and cheeks. This dreadful catastrophe occasionally occurs in famines both among children and adults. The sufferers are usually not only malnourished but also severely dehydrated as a result of diarrhœa or lack of nursing care. Large areas of the mouth and face may be destroyed before the patient succumbs. The only possible treatment is surgical excision of the dead tissues after a period of re-feeding and medical care. If the patient survives, plastic surgery may later help to correct the hideous deformity.

The terminal event in starvation is usually intractable diarrhœa. The atrophied intestinal glands and the paper-thin walls of the digestive tract are unable to digest and absorb properly even a bland diet, much less the kind of food on which people during famine may hope to survive, such as roots, leaves, and bread made from coarse grain. In almost all famines, outbreaks of diarrhœa have been reported, but bacteriologists have seldom found in the stools organisms that could be held responsible. Once diarrhœa has begun, it must be recognised as a serious sign. The fluid nature of the stools causes grave disturbances in water and salt balance which soon become incompatible with continued life.

Diagnosis

In times of famine the signs of starvation may be all too obvious, so much so that other causes of emaciation can be overlooked. However, a similar clinical picture may be produced by the cachexia of advanced cancer, tuberculosis, dysentery or other severe chronic infections.

Famine œdema must be distinguished from other primary causes of œdema—cardiac, renal or hepatic, and also from epidemic dropsy (p. 368). The distinction in a young child between simple starvation and kwashiorkor may be difficult. The two conditions are, of course, often both present in the same child.

Prognosis

Most people with primary subnutrition recover rapidly, once they have a free access to food. Appetites may be enormous. Over 5000 Cal./day may be consumed and be associated with a weekly gain in weight of 3 to 4 lb. In some patients, despite careful nursing and a good diet, low blood pressure and diarrhœa may persist. If, after one or two weeks, they show little improvement, this strongly suggests that irreversible changes in the myocardium or small intestine have developed and that the prognosis is therefore poor. After any severe famine there will be some who may linger on in this condition for many months if supported by good medical and nursing skill. But death rather than recovery is the usual end.

Treatment

In simple subnutrition, all that is needed is suitable food. Its management is more an administrative than a medical problem. When the patient suffering from starvation is seriously ill the nature of the treatment depends essentially on the facilities available. In this chapter we shall deal only with measures, which may be possible under famine conditions, when the nursing staff is inevitably limited and there are unlikely to be good laboratory facilities. Under these circumstances methods such as intravenous feeding have proved impractical and too dangerous to be justified. This and other special feeding methods which may be used when the number of patients is limited, the nursing staff sufficient and well trained and when expert laboratory help is available are described in Chapter 48.

Most famine victims, because of some alimentary dysfunction, cannot deal with large quantities of food. The patient's desire for food is often immense and no guide to his digestive capacities. Limitation of the food intake may be necessary. This is essential if there is nutritional diarrhœa or a severe degree of nutritional cachexia.

The choice of food is difficult. Many starving people in the prison camps of the 1939-45 war died from diarrhœa and collapse after the well-meaning attentions of those who rescued them. They were given any food that happened to be available—bully-beef, baked beans—which they could not readily digest. Only bland foods can be tolerated by the thin-walled intestines lacking essential digestive enzymes.

Probably the best food of all is **skimmed milk,** fresh or reconstituted from dried milk powder. The fat of the milk is better removed, because the pancreatic lipase needed for its digestion is a complicated protein ; its secretion may be greatly diminished if the body is seriously deficient in protein. Fats of all kinds intensify the diarrhœa from which so many starving people die.

Frequent small feeds of skimmed milk, 100 ml. or so at a time—as often as the patient is willing and able to take them—is the best way of averting death from starvation. This requires constant personal attention and nursing care. It is entirely impractical to prescribe for the needs of the patient in terms of calculated calories. Skimmed milk powders are normally reconstituted to give a mixture of 10 to 15 per cent. strength. However, if the patient is very weak, a more dilute mixture may be preferable. A variety of mild flavouring essences may be useful to stimulate the appetite. Slightly sour foods are usually acceptable ; yoghurt or other kinds of curdled milk may be tried. As the patient begins to recover he should be encouraged gradually to take semi-solid foods, along the lines followed in weaning a baby. With re-feeding there may be a temporary increase in œdema, especially if unlimited table salt is allowed, in which event the supply of salt should be temporarily restricted.

There may come a time in severe starvation when the patient, although still fully rational, refuses all food. The outlook is then very grave. Intragastric feeding (Chapter 48) then provides the only hope. Spectacular improvement may follow these measures, but some patients are beyond recovery.

Chapter 27

OBESITY

OBESITY is the most common nutritional disorder in present-day Great Britain and gives rise to more ill-health than all the vitamin deficiencies put together. The skill of a trained dietitian is invaluable in its treatment. Even if there were no other practical problems in human nutrition, the dietitian would more than justify her training and knowledge by the help she can give to fat people. A nation-wide attack on obesity would employ more dietitians than are at present registered by the British Dietetic Association. There is no reason to doubt that the same general statement is true for most other countries in Europe and North America.

Definition

While it is easy to define obesity as an excessive accumulation of fat in the storage areas of the body, it is difficult to state in individual instances the point at which this accumulation may be considered to be excessive. Gradual change in weight commonly occurs as age advances. Most individuals gain a few pounds in weight during the years from 25 to 40, while an even greater gain may take place in the succeeding decade. After the age of 50 to 60 there is usually a decline in weight. Obesity as a condition requiring treatment can be taken to be present when fat deposition has raised the body weight 10 per cent. or more above the standards discussed in Chapter 50.

Ætiology

Obesity can only arise when the intake of food is in excess of physiological needs. Some account of how appetite regulates food intake has already been given in Chapter 3. This regulating mechanism may be influenced by a variety of factors.

Age and sex.—Obesity may occur at any age and in either sex. In children both sexes are equally affected, but after puberty it is more common in women than in men. It is especially liable to arise after pregnancy and at the menopause.

Pregnancy.—A healthy woman may be expected to gain about 12·5 kg. (27·5 lb.) during pregnancy. About half of this represents the weight of the fœtus, placenta and uterus. Water retention in the tissues may account for 1 to 2 kg. The remainder can be attributed to an increase in adipose tissue, which serves as a store against the future demands of lactation. Many women gain more and retain this extra weight after the termination of lactation, thus becoming progressively more obese with each succeeding child.

Economic status.—In Great Britain obesity is probably more common among poor women than among the rich, perhaps because foods rich in fat and protein, which satisfy appetite more readily than carbohydrates, are more expensive than the starchy foods which provide the bulk of cheap meals.

Physical activity.—In all countries obesity is not often found in those who lead active lives and follow occupations or recreations demanding hard physical exercise. All those who have studied the problem (Swanson *et al.*, 1955 ; Johnson *et al.*, 1956 ; Stefanik *et al.*, 1959) have found that fat people do not generally eat more than thin people. They may even eat less. They also appear to be less physically active (Johnson *et al.*, 1956 ; Dorris & Stunkard, 1957). For instance Dorris and Stunkard got obese patients and comparable normal subjects to wear a pedometer for a week. The mean reading for the normals was 34·3 miles/week and for the obese 14·4 miles/week. With the mechanisation of industry and improved transport facilities, in particular the development and widespread use of motor vehicles, the proportion of people who take adequate exercise has declined and the number of sedentary workers, including office workers and business executives, has increased. The farmer who walked behind his plough using up 400 Cal. an hour now rides a tractor, using only 130 Cal. an hour. The housewife who used to wash clothes by hand, using 250 Cal. an hour now uses the washing machine at a fraction of that amount. Television, in so far as it may divert people from active recreation, will contribute to obesity. Hence inactivity may be a most important factor explaining the frequency of what has been described as 'creeping' overweight in modern Western societies. Although it is fashionable to decry exercise as a means of reducing weight, a combination of exercise and diet is to be strongly recommended.

Psychological factors.—There can be no doubt that some women often over-eat for emotional reasons. Naturally, this is a happy hunting ground for the deductive speculations of the Freudians. For the practical physician it is perhaps sufficient to know that some women over-eat because they are unhappy. They find solace in scones and cream cookies, for the same reasons that drive their husbands to seek relief in alcohol.

Eating habits.—The eating habits of obese people are variable. In some, continual nibbling seems to be an important cause of the excess food intake. These include many housewives who are fond of cooking and also others who work in kitchens. A night-eating syndrome has been described (Stunkard *et al.*, 1955) in which the patients suffer from a voracious appetite after the usual evening meal. It is often associated with insomnia and with marked anorexia in the morning. Some of these patients become extremely obese (over 230 lb.).

Genetic factors.—It is a matter of common observation that obesity runs in families. The nature of the genetic factors responsible is certainly not simple. Certainly several genes may be responsible for obesity in mice and perhaps also in man. Moreover it is difficult to distinguish their influence from those of family custom and eating habits.

Endocrine factors.—That obesity in women begins commonly at puberty, pregnancy or the menopause, suggests that endocrine factors may lead to a pathological appetite. Many obese patients excuse themselves with the comment : " My doctor says it's my glands " ; the general idea of an endocrine basis for obesity must therefore be popular with the medical profession. The clinical and experimental evidence in favour of this view obviously needs careful consideration. Failure of the sex hormones is sometimes suggested as the cause—on the analogy of the increase in body fat that follows castration in fat-stock animals—but obesity does not regularly follow secretory failure of the sex glands in either men or women. Failure of the thyroid gland is sometimes blamed ; but although some patients with myxœdema may be obese, others are of normal (or even less than normal) weight. At one time failure of the anterior pituitary gland was held responsible for obesity in young people, such as Mr Pickwick's fat boy (Fröhlich's syndrome). However, it is now recognised that the essential cause of this obesity is a disorder of the hypothalamus, as Fröhlich himself believed. This type of obesity may be analogous to that which follows hypothalamic lesions in animals (Chapter 3). Excessive secretion of growth hormone by the anterior pituitary gland is thought to be the cause of the ' large baby diabetes syndrome,' in which a mother gives birth to a large baby over 10 lb. in weight and—often many years later—herself develops diabetes. It is noteworthy that at the time of the infant's birth the mother is nearly always herself obese. While it can be confidently stated that a defective secretion of the well-known hormones of the thyroid, pituitary or sex glands is seldom the cause of obesity, it does not follow that endocrine factors, as yet undiscovered, may not be important. For instance, several ' fat-mobilising substances ' have been described. Thus Chalmers *et al.* (1960) have extracted a substance from the urine of starving human subjects which when injected into mice caused an increase in the fat content of the liver, a rise in blood lipids and in plasma ketones and also a fall in R.Q.—all evidence of fat-mobilisation. The production of this or other fat-mobilising substances could conceivably become reduced or deranged with resultant obesity.

Comment.—Interest in all the above factors should not be allowed to distract attention from the primary basic fact that obesity is always due to a greater consumption of food than the individual requires. Adipose tissue cannot come out of the air ; it can only come from food. A consistent excess intake of as little as 50 Cal./day can lead to a gain of 4 lb. over the course of a year. Fifty calories can be obtained from the following small amounts of food or drink : one ounce of lean meat or chicken ; one small potato ; half a slice of bread ; half a teaspoonful of butter ; half a glass of milk ; or quarter of a pint of beer. A similar result could occur from a small reduction in physical activity even if the daily calorie intake remained constant. In other words, the cause of obesity is too much food, too little exercise, or both.

Metabolism in obesity

There is certainly no reduction of energy expenditure by obese patients, though repeated efforts have been made to prove the contrary. Their basal metabolic rate is usually within normal limits and there is no reduction in the specific dynamic action of foodstuffs. There is no possibility that they succeed in extracting more calories from their food, because the absorption of food is about 95 per cent. efficient in normal thin people. Obese patients do not conserve energy by doing physical work with greater metabolic efficiency than normal ; in fact they have an expenditure of energy greater than normal, to move their weight about in day-to-day activities.

It has been suggested in the past that normal people manage to keep their weight within normal limits by virtue of some special ability for burning off any excess calories, perhaps in the small hours of the night. Failure of this mechanism might account for obesity. However, there is no good evidence that such a ' luxus Konsumption ' mechanism exists (Passmore *et al.*, 1955*a*).

Obese patients do not readily develop ketosis on a reducing regime. Many physicians have recorded this. Kekwick *et al.* (1959) measured the level of blood ketones after a period on a ketogenic diet and found little or no change in obese patients even after 10 days, whereas in normal controls the blood level rose markedly in 2 to 4 days. A biochemical explanation of this difference might go a long way towards an understanding of obesity.

There is no doubt that mice with some forms of genetical obesity have a metabolism that differs in many ways from that of normal mice (Mayer, 1953*a* ; Mayer, 1960). Mayer has shown that such mice when fed a diet containing isotopically labelled carbon, incorporate into the fat of their livers more of the isotope than do normal mice (Zomzely & Mayer, 1959). Slices of liver from such animals, when incubated *in vitro*, form fat from carbohydrate more rapidly than do liver slices from normal animals. There is thus an increased lipogenesis in this type of obesity. These animals, unlike normal mice, do not have a rise in blood ketones after a short fast.

In normal human subjects a short fast causes a rapid rise in the level of non-esterified fatty acids (NEFA) in the blood plasma. Gordon (1960) has shown that in many patients with obesity, refractory to dietetic treatment, this rise does not take place. This might be due either to a failure to mobilise fat normally or to a rapid rate of removal of NEFA that has been mobilised because of increased oxidation in the tissue. Evidence in favour of this latter view has been produced by Gordon using ^{14}C palmitic acid.

In conclusion, it must be admitted that at the present time it is not possible to define precisely a metabolic disorder causing human obesity. Nevertheless in our opinion there may be, in addition to overeating and underexercising, ætiological factors arising out of disturbances of physiological mechanisms, which regulate the metabolism of the tissues.

Adipose tissue and obesity

Excess fat is laid down in the adipose tissue of the body. This can be considered as an organ containing cells of mesodermal origin in which large quantities of lipids can be stored. As described in Chapter 6, these stores are being constantly turned over and adipose tissue is a metabolically active organ. Chemical analyses of samples of human adipose tissue have been undertaken by several workers. Thomas (1962) found that in biopsy samples from fifteen human subjects who were neither obese nor thin, the mean values were fat 82·8 per cent., water 13·5 per cent. and protein 2·6 per cent. As in studies conducted by other workers, she found wide variations in the amounts of fat, water and protein present in different samples. Adipose tissue from obese subjetcs was similar in composition and contained an average of 88·2 per cent. fat, 9·6 per cent. water and 2 per cent. protein. As the total weight of the adipose tissue in these obese subjects would be three or four times as much as in the controls, she concluded that in obesity not only was the adipose tissue more distended with fat, but there was also an increase in the total amount of cellular tissue. A similar conclusion was reached by Hausberger & Hausberger (1957), who analysed adipose tissue from normal and obese mice. Bjurulf (1959) examined human subcutaneous tissue histologically and concluded that individual differences in the thickness of the fat layer could be ascribed to differences in both the size and number of cells.

The available evidence thus indicates that probably both hypertrophy and hyperplasia of the cells are present.

Assessment of obesity

The traditional method is to weigh the patient ; the readings from a reliable balance compared with suitable standards described in Chapter 50 serve to distinguish the grosser cases.

An alternative method is the measurement with calipers of skinfolds, including the adipose tissue ; but as yet there is no general agreement about the best sites for making the measurements, and they take no account of the large amount of fat which may selectively accumulate in the omentum, within the abdomen. Another method which has been used for research purposes is to measure the thickness of the subcutaneous adipose tissue by radiological methods, but this method again merely records what the clinician sees for himself.

For research purposes, as distinct from the care of patients, it is possible to determine the total excess of lipids by the more precise methods discussed in Chapter 1.

Clinical features

The diagnosis should be made on the observation of the clinician who sees that there is too much adipose tissue in some part of the body. The distribution of this tissue is variable and attempts have been made to distinguish different types of obesity on the basis of it. It may be confined to the trunk, leaving the extremities slim, or, in the extreme case of the rare disease *progressive lipodystrophy* it centres round the hips and thighs, leaving the rest of the body thin or even emaciated.

As has already been said, the nature of the material that accumulates in the adipose tissue is not simply chemical lipid. Its composition is probably variable and in *Cushing's syndrome* for instance it may contain a high percentage of water.

Plate XIV shows two patients.

Complications

Apart from æsthetic considerations, obesity leads to mechanical disabilities, predisposes to metabolic and cardiovascular disorders, and so reduces the expectancy of life.

Psychological.—Æsthetic considerations are sufficient to make many people aware of the threat of obesity and anxious to avoid it ; those who do not succeed may become unhappy and a problem for their doctor. Thus obesity creates psychiatric problems in addition to any that may have been partly responsible for it.

Mechanical disability.—The structure of the human skeleton is not well adapted to carry an extra load, consequently flat feet and osteoarthritis of the knees, hips and lumbar spine are common in obese people. The abdominal muscles that support the viscera, and those in the legs which help by their contractions the venous return of blood to the heart, are infiltrated with fat. Hence their normal mechanical action is impaired, with consequent abdominal hernias and varicose veins. Adipose tissue around the chest and under the diaphragm is an obstruction to free breathing, with a consequent tendency to winter coughs and bronchitis.

Metabolic.—Obesity is associated with a number of metabolic disturbances. Diabetes mellitus arising for the first time in middle life occurs most commonly in obese people ; fortunately, however, the majority of obese people escape it. Obesity is often associated with an elevated level of cholesterol in the blood plasma ; perhaps in consequence, obese people develop stones in the gall-bladder more frequently than those of normal weight. Another site where cholesterol is deposited is in the inner lining (intima) of the arteries, producing atherosclerosis (Chapter 40). Gout is a rare disease that afflicts the obese more commonly than others.

Cardiovascular.—Apart from atherosclerosis, as already mentioned, obese people suffer from high blood pressure more commonly than those of normal weight. Fortunately it is usually of a benign kind, and since the patient is often unaware of its existence, he is best left in ignorance of its presence.

The work of the heart is increased by the extra mechanical work needed in moving the overweight body and in overcoming hypertension. This extra load on the heart, coupled with the tendency to atherosclerosis in the coronary arteries, no doubt accounts for the tendency to angina pectoris and cardiac failure among obese people in middle life.

The exceptional incidence of varicose veins has already been mentioned.

Skin.—The excessive deposit of subcutaneous fat predisposes to skin infections in the obese, particularly at the flexures, *e.g.* intertrigo below the breasts.

Accidents.—Obese people are often slow and ungainly; they are therefore liable to accidents of all kinds. At home they may trip over the carpet and spill kettles of boiling water over themselves; at their work they are slow to avoid the moving parts of machinery and in the street cannot quickly escape the traffic.

Life expectancy.—In view of these manifold complications it is not surprising that obese people are poor risks from the standpoint of life insurance. The statistics of the Metropolitan Life Insurance Co. (U.S.A.) have shown that for a man of 45, an increase of 25 lb. above standard weight reduces his life expectancy by 25 per cent. In other words he is likely to die at 60 when he might otherwise have lived to 80 had he not been obese. The risks of obesity in women are somewhat less.

Diagnosis

This apparently obvious disorder is frequently overlooked because the doctor is often preoccupied with one of its many complications. In addition many consulting rooms and hospital wards are still not equipped with reliable balances for weighing patients, and even when they are available they may not be used sufficiently. A regular practice of weighing patients and examining them for evidence of excessive fat deposits would prevent this. Some patients may appear to be of normal weight as judged by accepted standards, and yet may be obese. They are people with small hands, small feet and small bones; their obesity—often concentrated in the abdomen—will be missed unless they are examined. But a combination of weighing and physical examination is sufficient to make the diagnosis.

Obesity should be distinguished from normal causes of an increase in weight. Every now and then the diagnosis of pregnancy is missed, and this creates embarrassment. Athletes in training are sometimes considerably overweight as judged by normal standards; their extra weight is due to muscular hypertrophy.

Another important cause of gain in weight is œdema resulting from cardiac, renal or hepatic failure. Œdema does not generally become manifest until the extracellular fluid is increased by 10 per cent. or more, so that the initial gain in weight may be mistaken for a tendency to obesity, if the patient is not properly examined for evidence of the underlying causative disease.

In myxœdema there may be a sufficient accumulation of myxœdematous tissue to cause excessive weight. The material in this tissue is not fat, but a protein resembling collagen in biochemical characteristics.

TREATMENT

General

The obese person will look fitter, feel better and have a better chance of keeping well and living longer if she reduces her weight to the normal standard for her age, sex, height and occupation.

The *first essential* is for the patient to understand the reasons why she should reduce her weight. She must be convinced that she must give up permanently those habits which have led to obesity ; otherwise the reduction in weight which she can expect to obtain from an anti-obesity diet will not be maintained when dietary restrictions are somewhat relaxed. In every case of obesity, income exceeds expenditure, and rational treatment must correct the balance.

The *second essential* is to eradicate false knowledge, often acquired from popular papers and books.

The *third essential* is to instruct the patient in some elementary physiological principles in regard to appetite, exercise and the expenditure of energy.

The *fourth essential* is to teach the patient about the caloric value of different foods. It must be made clear that there are no ‘ slimming foods ’ and no successful ‘ slimming diets ’ which do not depend on a reduced intake of calories. *The essence of treatment is to reduce the quantity of food eaten.*

The patient should know at the outset the kinds of foods which she is likely to eat in excess and which therefore may contribute largely to the obesity. These are often bread, cakes, pastry, thick soups and fried foods. She should also learn that snacks or apéritifs taken between meals cannot be permitted. Chocolate, sweets, cocktail ‘ pieces,’ beer, stout and other alcoholic drinks all add to the caloric intake.

The successful treatment of obesity requires a strict regimen. This is often difficult for people with irregular habits with regard to both food and exercise, such as many doctors, commercial travellers and company directors. An evening with friends, a business lunch, a banquet, if care is not taken, may undo the good habits established by weeks of conscientious dieting. In Edinburgh, a few weeks after the celebration of Hogmanay the contrite patients begin to return for further dietetic advice.

The essential regimen for the treatment of obesity is to regulate the daily intake of calories. It is therefore wise that every patient should at first make a practice of weighing what they are about to eat. This must be continued until they become accustomed to judging correctly quantities of food. A suitable balance for this purpose, on the sideboard or kitchen table, is needed. Adherence to an exact diet necessitates good discipline.

Diets must not depart too much from established food habits. An obvious absurdity may be to advise an obese rice-eating Indian to take for breakfast one thin slice of wheaten bread. He may not take any breakfast, and wheaten bread may be unavailable. This is where the art of the trained dietitian comes in; to provide a diet of proper composition suitable to the needs and habits of the particular patient. A printed diet sheet, handed out to a patient at a single interview without adequate discussion and explanation, seldom achieves results.

The diet

Energy output has been determined with great accuracy for people undertaking various activities. To keep in caloric balance a person doing sedentary clerical work will require about 2000 to 2500 Cal. daily, a person doing light work 2500 to 3000 Cal., while a person doing heavy work, such as felling trees, may need 4000 Cal. or even more. It is obvious therefore that dietary requirements vary greatly according to occupation and that a business executive might require only about half the caloric needs of a heavy manual worker.

An obese middle-aged housewife will usually lose weight satisfactorily on a diet providing about 1000 Cal./day, such as Diet No. 1. This is based on sound physiological principles. If her daily energy expenditure is 2200 Cal./day the negative balance will be 1200 Cal. The caloric value of obese tissue is about 7·5 Cal./g. The weekly negative caloric balance is therefore equivalent to $\frac{1200 \times 7}{7{\cdot}5}$ g. or 1·1 kg. (2·4 lb.). A weekly weight loss of 2 to 3 lb. should be the general aim.

Protein.—The protein content of the diet should be sufficient to maintain the body in nitrogen equilibrium. Usually 60 g./day (or even less) is sufficient for this purpose. Some weight-reducing regimens (*e.g.* that of Banting) have been based on the principle of eating mostly meat and other foods rich in protein. Some scientific support was given to this principle by the knowledge that proteins stimulate specific dynamic action and should encourage the dissipation of surplus calories. High protein diets may readily satiate appetite, but are very expensive and so seldom practical.

Carbohydrate.—The intake of foods rich in carbohydrate should be drastically reduced since over-indulgence in such foods is the most common cause of obesity. There have been unfounded fears that too drastic reduction of the carbohydrate intake may lead to ketosis and that this ketosis is responsible for numerous complaints such as headache, weakness and nausea, sometimes made by obese patients when first faced with the necessity of dietary restriction. In fact, obese people seldom develop more than a trace of ketosis on any diet and never sufficient to cause symptoms.

In a diet of 1000 Cal./day, 100 g. of carbohydrate is a suitable allowance.

Fat.—A diet providing 1000 Cal. and containing 100 g. of carbohydrate and 60 g. of protein, cannot include more than 40 g. of fat. This allowance of fat, though small, is sufficient to make the diet palatable and acceptable to the patient.

Recently popular books and newspaper articles have stated that there is no need to restrict the intake of fat in obese patients. " Eat fat and get slim " is advice which has an obvious appeal. It arose from the observation of Kekwick and Pawan (1956) who found that when patients are treated in hospital on 1000 Cal. diets, the initial weight loss is greatest if almost all the calories (up to 90 per cent.) are supplied in the form of fat. This observation is of considerable scientific interest, but has no therapeutic value. As the authors point out, patients could not be expected to remain on such a bizarre diet containing little else but butter, cream and olive oil, for more than a few days. A probable explanation of the observation is that the rapid but temporary loss of weight which was as much as 2 to 4 kg. in a few days was due to loss of water. Similar rapid losses of weight occur in the first three days of complete starvation.

Passmore (1961*b*) has pointed out that the common factor between a high fat diet and complete starvation is absence of carbohydrate. He has put forward the thesis that the water content of the body depends on the nature of the fuel mixture being metabolised in the body. When carbohydrate is the main fuel, the human body requires 2 to 4 kg. of water in the tissues more than when fat is being utilised. This water is at once lost when dietary carbohydrate is restricted. All popular ' slimming regimes ' involve a restriction in dietary carbohydrate and in this way it is possible to explain their immediate, but only temporary, success. Continuous reduction of weight can only be brought about by a continuous restriction of total calorie intake below the level of energy expenditure.

Vitamins.—A properly constructed reducing diet should contain plenty of green vegetables and fruits, since they contain few calories, while their bulk helps to fill the stomach and relieve hunger ; they also help to relieve constipation which is a common trouble on a low food intake. Their vitamin A and vitamin C activity will be sufficient to meet the body's needs. With meat, fish and eggs in the diet and little or no refined cereals and sugar, it is improbable that deficiency of any component of the vitamin B complex will arise. A good reducing diet will meet the patient's needs for vitamins. Multi-vitamin tablets are an unnecessary expense for most patients. Any doctor who has doubt about the vitamin intake of a particular patient should recommend in the first instance some natural source of the vitamin B complex such as yeast extract (*e.g.* Marmite) or wheat germ (*e.g.* Bemax).

Minerals.—The only minerals that need serious consideration are calcium and iron. Provided that the diet includes half a pint of skimmed milk, there is little likelihood of a negative calcium balance in an adult. The supply of iron is less sure. In the treatment of obese patients—as indeed of all others—the doctor must be constantly on the alert for the earliest signs of anæmia.

Water and salt.—At one time patients were often advised to restrict their intake of water, but there is no sensible reason for keeping fat patients thirsty by denying them ordinary desires for fluids. Plain water or unsweetened tea can be taken but not sweetened 'juices.' Alcoholic drinks are a source of calories and, if taken, a corresponding reduction in the diet is necessary.

In obese patients with œdema from congestive heart failure or other causes, there will be both water and sodium retention. For all such patients, salt restriction is necessary and suitable diuretics should be given (p. 568).

Diet No. 1 is in general suitable for the treatment of an overweight middle-aged housewife in Great Britain. But it may be unsuitable in other circumstances and in other climates. Dietitians with knowledge of food values and local eating habits can achieve a great deal of good by devising diets, suitable to the established customs of their own community, which also provide about 1000 Cal. made up from about 60 g. protein, 100 g. carbohydrate and 40 g. fat. An obese man engaged in active work cannot tolerate so little and will lose weight on about 1500 Cal.

Proprietary powdered food products.—Recently a vigorous advertising campaign has been instituted by various firms recommending their products for the treatment of obesity. These products contain a balanced mixture of protein, carbohydrate and fat with the addition of essential vitamins and minerals. Half a pound (230 g.) of one proprietary preparation is stated to provide 900 calories daily. It is mixed with a quart of water and taken in divided quantities at four, five or six feeds in the day. On such a diet the loss of weight will be similar to that achieved by a patient partaking of a 900–1000 Cal. diet made up of natural foods, as recommended in Diet No. 1. Since these proprietary food products are more expensive, less palatable and more monotonous than this diet, they are not recommended for the routine treatment of obesity. If, however, patients are unable or unwilling to learn the basis of the calorie value of the different foods or will not take the trouble to weigh articles of food, or if experience shows that the patient has not the will power to take only the amounts of food prescribed for him, then a trial of one of the proprietary powdered food products is justified.

Exercise

The value of physical exercise has probably been underestimated. It is sometimes stated (but without evidence) that exercise promotes appetite in excess of caloric needs and so may aggravate obesity. But there is evidence from experiments on animals that the reverse is true. A certain minimum amount of exercise may be necessary for the accurate regulation of food intake by the appetite (p. 43).

Most obese patients lead sedentary lives and the full extent to which urban and industrial life restricts activity is only now being realised. In many obese patients it is impossible to prescribe anything but the mildest of physical exercise. Walking, however, is good exercise and an hours' walk at 3 miles an hour will expend about 300 Cal. (or more for a heavy person) which represents approximately the calorie value of one ounce of fat. This may seem a very small amount to worry about, but an intake of 1 oz. of fat daily, if additional to one's maintenance requirements, could mean an increase in weight of over 20 lb. in a year. There is little doubt that most obese people would be improved by exercise, *e.g.* walking, swimming, gardening, provided it does not exceed their cardiovascular capacity. All obese patients, whose occupation is entirely sedentary, should be advised to walk for at least an hour a day, always provided they are fit to do so. Regular *daily* exercise is much more valuable than spurts of activity at the week-end.

The benefits of exercise must not distract attention from the diet. Treatment often involves changes in both the diet and manner of life.

Intensive treatment

The regimen of dietary restriction and physical activities, already described, aims at achieving a rate of weight loss of just over 1 kg. or 2 lb. a week. Very fat patients would have to persist with such a regime for many months before achieving a satisfactory weight loss. Such slow progress may be disheartening and lead to the abandonment of treatment. Provided there are no orthopædic or cardiovascular complications, it is possible to increase the physical activities and cut down the diet still further. Patients have been kept for up to 6 weeks on diets providing only 400 Cal./day, whilst they walked 10 miles daily (Strong *et al.*, 1958). This regimen involved negative balances of the order of 3000 Cal./day. The patients lost weight at rates of up to 3 kg. or 7 lb. a week, yet they remained fit and well able to carry out the exercise. Ashley and White (1961) have also kept obese patients for long periods on diets providing 500 Cal./day or less with no adverse effects and good immediate results. Their paper contains a valuable review and discussion of the effects on the chemical composition of the body. A period of fasting with complete abstinence from food for as long as 10 days at the onset of treatment has been recommended by Bloom (1959). It should only be tried in young patients without complications.

Such regimens are clearly contraindicated for middle-aged or elderly patients. The long-term results of such treatment cannot be stated until more experience has been gained. They may occasionally be valuable for selected young obese patients, particularly as a demonstration of what can be achieved with sufficient discipline.

The majority of obese patients will do well if they persist in a regimen of one hour's walk and a diet of 1000 Cal./day, and this is the regimen which we recommend.

Other physical measures

Turkish baths, massage—even colonic lavage—have had their popularity as means of reducing weight. Though they achieve a temporary success in bringing the weight down by a few pounds, this is due solely to loss of body water which is very soon replaced. They provide no escape from the inevitable necessity of dietary restriction.

Drugs

Anorectic drugs.—During the past 100 years a great many drugs have been recommended as ' slimming agents.' Modern criticism has disposed of the claims made on behalf of all of them except a group known as the ' anorectic drugs,' which are all related chemically to amphetamine. The value of these drugs in the treatment of obesity is at present undecided. Pharmaceutical firms in several countries market these drugs under a bewildering variety of proprietary names, but all are chemically related to amphetamine and probably have the same pharmacological action. Doctors are exposed to intensive advertising campaigns setting out these claims. For this reason it is necessary to consider their mode of action. The subject has been reviewed at length in an article by Modell (1960) in the *Journal of the American Medical Association* and discussed in an Editorial and the correspondence column.

Amphetamine certainly stimulates the higher cortical centres. In this way it may overcome depression and create a sense of well-being which may help the patient to persevere with a dietary regimen to which he is finding it hard to adhere strictly. Modell considers that any benefit that patients may derive from the use of these drugs arises secondarily to an improved psychological outlook. The view widely held by physicians is that amphetamine has a direct depressive effect on appetite. In support of this view is a report from a good physiological laboratory (Brobeck *et al.*, 1956) which describes a stimulating effect of amphetamine on the electrical activity of the satiety centre in the hypothalamus of cats, but no effect on the nearby feeding centre. Should a specific action of the drug on a centre inhibiting food intake be substantiated, it would strengthen the case for its use in the treatment of obesity. However, it would not alter the fact that there are serious disadvantages to the use of amphetamines. They may cause insomnia, irritability and serious disturbances of behaviour; in addition they may lead to an increased heart rate, raised blood pressure and other evidence of excessive activity of the nervous system. They can give rise to habituation or even addiction. To overcome some of these disadvantages several proprietary preparations have been introduced which contain an anorectic drug together with a sedative or tranquilliser. In such a compound preparation it is impossible to alter the dose of either constitutent independently of the other, and this is most unsatisfactory. If it is desired to counteract the stimulating effects of amphetamine, it is advisable to prescribe sedatives separately.

Several controlled clinical trials of anorectic drugs have been carried out, including two in Edinburgh (Duncan *et al.*, 1960; Hampson *et al.*, 1960). In both of these it was shown that phenmetrazine (25 mg. twice daily) produced a small increase in the rate of loss of weight in a group of obese patients on an orthodox reducing regimen as compared to a control group on the same regimen. To demonstrate this effect, large numbers were employed with the usual statistical appurtenances.

Anorectic drugs are no substitute for a dietary regimen. At best they are an aid which may help some patients to adhere more strictly to their diets. It is never justified to use these drugs at the beginning of treatment. If an obese person has failed to adhere to a diet despite efforts to do so, then the use of an anorectic may be considered. The drug should be prescribed for periods up to four months, after which it loses its effect. There is no evidence that any of the expensive proprietary drugs are more effective than the B.P. tablets of amphetamine or dexamphetamine. The usual dose is one tablet (5 mg.) two or three times a day before meals. If insomnia results, this may be overcome by giving a suitable barbiturate at bed-time.

Other drugs.—Thyroxine stimulates metabolism and for this reason it has had an extensive trial in the treatment of obesity. There is no doubt that its use is contraindicated except in those rare cases in which obesity is associated with clinical evidence of a deficiency of secretion by the thyroid gland. In euthyroid people thyroxine produces no significant increase in metabolism unless given in toxic doses which cause tremor, nervous diarrhœa, palpitation and tachycardia. The latter is particularly undesirable in elderly patients with myocardial weakness. Hence the administration of thyroid extract or thyroxine to obese euthyroid patients is not only useless but is potentially dangerous.

Dinitrophenol is a drug which increases oxygen uptake, and once enjoyed a short vogue as a slimming agent. It is extremely toxic and its use is strongly contraindicated.

Methyl cellulose is an indigestible substance which adds bulk to the diet. It will distend the stomach and so may help to allay hunger. In clinical trials it has not been shown to have any effect in promoting weight loss, and it is very doubtful if this product is of any value as an adjunct to dietary therapy. However, it is quite harmless.

Sedatives and tranquillisers can play no part in the treatment of obesity *per se*. However, they may be useful for some obese patients who suffer from an anxiety state.

Diuretics have been extensively tried in the treatment of obesity. They are of no value in promoting weight loss unless, in addition to the excess adipose tissue, the patient has œdema due to cardiac failure or other organic disease.

Surgery in the treatment of obesity

Plastic surgeons have sometimes been called upon to assist in the treatment of obesity. Thus it is possible to reduce and resuspend enlarged and pendulous breasts. For some patients this has proved a satisfactory operation. Sometimes there may be justification for excising a pendulous abdominal wall (Plate XIV). In such patients even after successful removal of the fat by dietary restrictions, the skin may remain undesirably lax.

Plastic operations have also been carried out with the object of improving the shape of the thighs and arms. Such operations are probably contraindicated. While the plastic surgeon can produce an immediate temporary improvement in the appearance of either arms or legs, the fat may reappear, in which case it is laid down in irregular lumps in the subcutaneous tissues of the limbs. The last state of the patient is then far worse than the first.

Prognosis

It is easy for an obese person to lose up to 10 lb. in weight. This accounts for the temporary successes of numerous popular ‘ slimming cures.’ How difficult it is to achieve long-lasting losses is not generally realised. Stunkard and McLaren Hume (1959) have reviewed the published results of seven obesity clinics in the U.S.A., each under the direction of physicians who were experienced and interested in the treatment of obesity. Taking as an index of success the loss of 25 lb. or more, satisfactory results in these clinics ranged from 12 to 28 per cent. With a stricter standard (the loss of over 40 lb.) the successes amounted to only 2 to 8 per cent. In Edinburgh, Rose (1959) reported a large number of failures. In a series of 407 patients, 148 (36 per cent.) did not report again after the first interview and only 15 per cent. were discharged after having achieved the desired loss of weight.

Experience in many clinics has also shown that it is difficult for patients to maintain their reduced weight after successful treatment.

The reasons for these poor results are not clear. Perhaps the failure of doctors to appreciate the complicated and difficult problem presented by each obese patient is a contributory factor. Stunkard and McLaren Hume comment on their findings as follows : “ It was the rare physician who entertained the possibility that failure to follow a regimen might in itself be a medical problem. Rarely have physicians so readily surrendered a part of their domain to moralising indifference and despair. . . . The naïve optimism of the medical profession about the treatment for obesity has been widely accepted by the lay public. Most obese persons feel that they should be able to lose large amounts of weight in a short time and with little discomfort. When they find that these expectations are not realised and when they encounter the irritation of their physicians over their failure, they turn to any agency which promises results. The profusion of non-medical agencies testifies to the extent of our patients’ needs and to the magnitude of our failings.”

For these reasons it is most important that doctors, assisted by dietitians where possible, should supervise carefully and persistently the details of the management of each patient. The best way of reducing the number of failures is to encourage patients to persevere with the reducing regimen and to report to their medical adviser or dietitian at regular intervals as described below.

Management

With proper dietetic advice and regular interviews the majority of obese patients should lose weight satisfactorily provided they carry out conscientiously the instructions in regard to diet and exercise.

No known drug provides an easy alternative to the discipline of a strict dietary regimen. The patient should weigh herself at weekly intervals ; day-to-day variations in weight are not important : they may be due to retention of urine or fæces, or to the increase in body water that frequently precedes menstruation. The patient needs to be seen at regular intervals. After a weight-reducing diet has been prescribed, she should attend at first perhaps every fortnight and later every month or so. The object of these visits is threefold.

First, to check progress. At each visit the patient should be weighed. A good balance is necessary. Spring balances are unreliable and need frequent checking. Lever balances are good and need checking only once a year. A doctor can keep no more useful record of his patients than that of their weight, measured at regular intervals. If the weight loss has exceeded 3 lb./week some addition to the diet may be permitted, such as an additional thin slice of bread (1 oz., 15 g. of carbohydrate, 70 Cal.). The initial weight loss is often dramatic and frequently mainly due to loss of water, but it impresses the patient. Thereafter it often slows up, due sometimes to waning interest, but perhaps also to the same physiological adjustments to a lower caloric intake as happens in underfed people (p. 373).

Secondly, to encourage the patient. If the weight loss has been satisfactory, simple assurance of the need to persevere is all that is necessary. If it is not, then every art of persuasion may be needed—reasoning, begging and even mild bullying.

Thirdly, to check the patient's general health. If weight loss is not proceeding satisfactorily, a constant watch for the complications of obesity must be maintained. If any complications, orthopædic, metabolic or cardiovascular, are present, regular supervision is necessary. If the patient suffers from one of these, persuasion to persevere with the regimen is easier—for promise of relief from the distressing symptom can be given if only the patient will lose weight.

It is difficult sometimes to decide how long to continue a regimen. It is probably unwise to 'tailor' every obese patient to the standards laid down in Chapter 50. Nevertheless, the nearer a middle-aged woman can get back to her standard weight, the better chance she has for a healthy and happy future. Once a satisfactory weight has been achieved, discipline can be only partially relaxed. Many unfortunate people exist for whom the slightest dietary relaxation results immediately in a rapid gain in weight ; for them there is no alternative but life-long attention to a restricted food intake, and it is here that the advice and encouragement of a doctor or dietitian can be most helpful.

Finally, there are those who fail to lose weight despite regular encouragement and the best dietetic advice. Amphetamine or phenmetrazine may be helpful in such cases. In the last resort, admission to hospital or nursing home may be the best advice, with the attentions of a skilled dietitian who will prove to the patient that loss of weight is possible with proper regulation of the food intake. Diets providing as little as 400 Cal./day can be used with success for this purpose, and with proper care no harmful effects will follow.

Prevention.—Prevention of obesity rests with the doctor who early discerns when his patients are beginning to put on too much weight. Young mothers especially are apt to do so during and after a confinement. One of the most useful records that a doctor can keep about his patients is that of their weight, measured at regular intervals. Sudden, unexplained changes may not only warn of the threat of obesity, but, in the opposite direction, can be the first indication of other diseases in their earliest stage.

It is a guiding principle in medicine that prevention is better than cure. Accordingly the following points for the prevention of obesity should be made clear to all who are liable to become over-weight.

(*a*) *Remember* that under-exercising and over-eating are the causes of obesity. Regular exercise should be an essential part of the reducing regimen not only because of the fat that exercise burns up but because exercise is of great value in keeping the body healthy. The motor vehicle is at the same time a great boon and one of the great medical dangers to modern man. Always walk as much as possible every day.

(*b*) *Remember* that calories are the key to the weight problem.

(*c*) *Remember* that you can eat what you like and grow thin provided you make sure that your caloric intake is less than your caloric expenditure.

(*d*) *Remember* that mental work does not require additional calories.

(*e*) *Remember* that alcohol may be an important factor in the causation of obesity. Alcohol is used by the body solely as a source of energy and thus it frees an equivalent number of food calories which are then stored as fat. Few people realise that a large whisky or gin, or a pint of beer, is the caloric equivalent of two medium-sized eggs, or one glass of milk, or a medium-sized slice of bread and butter, or an average helping of potatoes.

(*f*) *Remember* to weigh yourself regularly, say once a week. This is essential if you are to find out in good time that you are putting on weight—and it will show how successful are your efforts to reduce overweight. Use the same scales and always weigh yourself either naked or in approximately the same clothes.

(*g*) *Remember* immediately to put into operation the necessary measures to reduce weight—increasing expenditure of energy by added exercise and reducing caloric intake by cutting to the minimum the intake of butter and foods rich in fat, and the carbohydrate-rich foods such as bread, cakes, potatoes, sugar and thick soups. Feed mainly on foods low in calories such as clear soups, lean meat, chicken, white fish, green and yellow vegetables and fresh fruits. By making small but essential adjustments in one's eating habits, obesity can usually be prevented. No diet sheet is required but some knowledge of the caloric value of different foods is necessary. For this purpose instruction by a dietitian is of great value. The longer the delay in taking the necessary steps to prevent the development of obesity, the more unpleasant, lengthy and strict will be the dietary restrictions required for its correction. Hence the need for regular weighing so as to be warned of what may be occurring insiduously.

Conclusion

It is foolish for people to attempt to ' slim ' on their own initiative without proper advice. A qualified dietitian can provide one of the most useful ancillary services to medicine by giving her time and her detailed knowledge of nutrition to the practical problems of treating obesity. The relief of so many common ailments, such as backache, sore knees, winter coughs—even angina of effort—are all part of the rewards of a dietitian's skill. But it is clearly sensible that she should always work in collaboration with a doctor. Everyone should know of the undesirable and potentially dangerous complications to which overweight persons are more liable than those of normal weight. Everyone must decide for himself whether he wishes to take these risks or not. Since the immediate causes of obesity are over-eating and under-exercising, the remedies are available to all, but many patients require much help in using them.

Chapter 28

KWASHIORKOR

Protein-Calorie Deficiency Disease

KWASHIORKOR is a nutritional deficiency disease due predominantly to an inadequate intake of utilisable protein, occurring principally in children shortly after weaning and characterised by muscular wasting, œdema, irritability or mental apathy, failure to grow and a liability to a damaged liver.

The fundamental biochemical lesion is caused by a deficiency of amino acids necessary for protein synthesis. Hansen *et al.* (1956) treated children with typical features of the disease, using a mixture of eighteen amino acids, free of vitamins. They observed full ' initiation of cure ' in some of these patients. It is not as yet possible to state the relative importance of lack of individual amino acids.

The immediate cause of the disease is often an acute infection (*e.g.* measles or gastroenteritis) ; this increases the rate of breakdown of tissue proteins and also may decrease the dietary intake of protein.

Excellent general reviews have been provided by Brock and Autret (1952), Rao *et al.* (1959), Waterlow *et al.* (1960) and Scrimshaw and Behar (1961).

History

Cicely Williams (1933) was the first to record that ' some amino acid or protein deficiency ' might be an ætiological factor in *kwashiorkor*, the name given to this disease by the Ga tribe living in and around Accra, the capital of the Gold Coast (now Ghana). Later, Dr Williams (1958) wrote that the definition of kwashiorkor which was originally given to her is ' the sickness the older child gets when the next baby is born ' ; this translation indicates the circumstances in which the disease most commonly develops, namely an ignorance of the best foods to give children during the weaning period, or an inability to provide them for one reason or another. She noted that the same condition has been described in 1906 in Germany, in 1924 in Indo-China, in 1926 in Mexico and in 1928 in East Africa. In fact the disease occurs in any part of the world if the dietary conditions described below are present. Elsewhere in Africa doctors have frequently misinterpreted the descriptive term ' kwashiorkor ' to mean ' red boy ' or ' pale-coloured child.' Children suffering from kwashiorkor frequently have pale-coloured skins and mucous membranes and depigmented, but seldom red, hair. Reddish-haired children and adults are not uncommon in African communities. However, this condition is of genetic origin and only associated by chance with protein malnutrition.

Descriptive names for this syndrome which have been used in the past 25 years by clinicians include ‘ infantile pellagra,’ ‘ malignant malnutrition,’ ‘ syndrome dépigmentation-œdème,’ ‘ distrofia pluricarencial.’ The Joint FAO/WHO Expert Committee on Nutrition (1961*b*) decided that ‘ protein-calorie deficiency disease ’ was better suited to describe its basic ætiology than ‘ kwashiorkor.’ However, the Ghana word seems well established in the international medical literature, and like the Malayan ‘ beriberi ’ will probably hold its own against more scientific newcomers.

Ætiology and incidence

As with other deficiency diseases all the clinical features cannot be attributed to a single dietary defect ; but there is little doubt that the predominant features are due to a deficiency of protein, either absolute or relative to energy requirements. The importance of the caloric value of a diet to ensure optimum protein utilisation has been pointed out in Chapter 5. At periods of life when there is great need for both protein and energy to meet the demands of growth, as in infancy, childhood and at puberty, or during pregnancy and lactation, dietary restriction of either protein or calories, or both as is most often the case, will precipitate the development of kwashiorkor. If the customary diet of a population is limited in protein and calories to around the levels of minimal requirements, the disease may be precipitated in epidemic proportions by outbreaks of febrile illnesses such as malaria, measles or whooping-cough. A helminthic or other infection may bring out the disease in a child belonging to a family whose diet is barely adequate. Here are good examples of the importance of consuming a recommended allowance of any nutrient which provides a safety margin above the minimum requirement for growth and maintenance. In addition, failure to utilise properly such dietary protein as is available may result from a lack of digestive enzymes, itself caused by a quantitative or qualitative deficiency of dietary protein.

The syndrome has been described at all ages and in both sexes. Undoubtedly it is most common in those infants or toddlers whose mothers wean their children from the breast on to diets which are mainly composed of starchy gruels containing too little protein and providing too little energy. This may be on account of ignorance of good nutritional practices or lack of money to buy better foods. In the less-developed countries, where the majority of the world’s population live, such mothers too often do not have ready access to suitable protein-rich foods with which to supplement these gruels.

Kwashiorkor is a rare disease in countries in which literacy, education and developed food-processing industries have made it possible for all classes of the population to obtain and consume diets which provide sufficient energy and nutrients. Occasional cases are encountered in New York, Paris, London and other cities which include among their populations immigrants from less-developed countries. Such people are unaccustomed to urban living conditions and are inexpert in purchasing diets suitable for the younger members of their families.

In the rural areas of many underdeveloped countries families grow their own food and employ methods of crop culture and food processing adapted over the centuries by circumstances to be compatible with the continuing existence of the community. Many traditional methods of crop production and food preparation must be commended and should be retained. Others should be modified and made more effective by the introduction of new techniques suitable to local conditions. Although food supplies may be sufficient in these rural areas, cases of kwashiorkor occur, often as the result of failure to comply with traditional dietary habits for reasons outwith the control of the family group. For instance a mother may die, or develop breast abscesses and her milk fail, when her child is a few weeks or months old ; no aunt, grandmother or grand-aunt may be in lactation at this critical time to act as a foster-nurse. In many rural areas the food supplies may become scarce each year in the season before the harvesting of the staple food, and the incidence of kwashiorkor may increase at this time. The incidence of kwashiorkor in children from birth to nine years of age, living in the rural areas of Nigeria, was found by Nicol (1959) to vary between 2 and 5 per cent., being highest in areas where the staple foods are yams, cassava or other starchy tubers, and lowest where cereals such as sorghum and millets (*Sorghum vulgare*, *Pennisetum typhoideum* and *Eleusine coracana*) provide most of the dietary calories and protein. The incidence of kwashiorkor in other African countries is probably of the same order, most cases occurring between the ages of 1 and 4 years.

A much higher incidence of kwashiorkor may be found in the rural areas of countries which are much more densely populated than those of the African continent, such as the Indonesian islands and Bengal in India, and also in rapidly growing towns in the tropics. Here, lack of land to grow sufficient foodstuffs to provide the customary diets, and the high cost in the city markets of protein-rich foods, whether fresh or processed, are factors additional to lack of nutritional knowledge, seasonal food shortages and misfortune which operate to produce the syndrome. Pædiatric wards in city hospitals usually contain severe cases of kwashiorkor, and the out-patient departments treat many more patients who are less seriously ill.

Pathology

The inadequate supply of amino acids leads to a failure of protein synthesis in the tissues, which prevents the normal development of all the organs of the body.

Body composition.—The total body water has been measured in children with kwashiorkor by Schnieden *et al.* (1958) in Nigeria, and by Smith (1960) in Jamaica. In several children more than 80 per cent. of body weight was found to be water. A child aged 1 year with kwashiorkor may weigh only 5 kg.—half the weight of a normal child. Of this, 4 kg. may be water and so the total protein content may be less than 1 kg. The child with kwashiorkor may have laid down only one-third as much protein as a normal child. Many children with the disease may be grossly emaciated and have little or no subcutaneous fat. If, however, the child has received plenty of carbohydrate in his diet, then he may be plump, and fat may be present in normal amounts.

Failure to synthesise serum albumin.—This is always low. Dean and Schwatz (1953) found an average value of 1·51 g./100 ml. (range 0·76 to 2·17), which rose to the normal value of about 3·5g./100 ml. in response to treatment. This rise is a useful index for assessing the response to different methods of treatment. The low level of serum albumin is almost certainly in part responsible for the œdema which is frequently present. However, as in famine œdema, the relation between the biochemical change and the clinical sign is not clear cut and other factors (p. 376) may contribute to the water retention.

By contrast the level of serum globulin is usually well maintained and the gamma globulin fraction is often higher than normal (Rao *et al.*, 1959), which is probably due to the presence of infection.

Synthesis of hæmoglobin is also impaired, but seldom sufficiently to cause severe anæmia, and hæmoglobin levels are usually between 7 and 10 g./100 ml.

Failure to synthesise digestive enzymes.—The cells of the digestive glands, notably the pancreas, atrophy and can no longer produce enzymes in normal amounts. Thompson and Trowell (1952) aspirated the duodenal contents and measured the concentrations of pancreatic enzymes present. They found very low values for amylase, lipase and trypsin in children with kwashiorkor. Levels rose to normal after treatment. This failure to make digestive enzymes is probably largely responsible for the gastro-intestinal disturbance and diarrhœa which are so commonly present.

Electrolyte disturbances.—The diarrhœa can cause losses of potassium of 20 to 30 mEq./day (Hansen, 1956). Magnesium is also lost in large amounts (Montgomery, 1961). These cations are drained away from the tissue. Sudden death may occur due to heart failure from potassium deficiency. Sodium deficiency is also common, aggravated in hot countries by excessive losses in the sweat.

Failure to maintain normal liver structure.—A severe fatty degeneration of the liver may be present. The technique of liver biopsy has enabled a clear-cut picture to emerge of the changes that take place as the disease progresses. In early cases there is an accumulation of small droplets of fat within the liver cells at the periphery of the lobules. The droplets increase in size and extend from the periphery towards the centre of the lobules. In fatal cases all the liver cells may be filled, each with a big fat droplet pushing aside the cell nucleus and reducing the cell cytoplasm to a narrow rim. The Gillmans (1951), who give an excellent account of the histological changes, show striking microphotographs of liver sections in the advanced stages which, as they point out, could be readily mistaken for sections of perirenal fat. Cellular infiltration of the portal tracts accompany the fatty changes. Chemical analyses of liver biopsy material reported by Waterlow and Weisz (1959) indicate that one-third of the liver protein may be lost. Nevertheless, liver function tests are usually only a little below normal. Liver failure is seldom responsible for death.

On treatment the fat is usually removed from the liver, which returns to its normal structure. The livers of young children have immense reserves of function and great capacity for healing.

Failure to maintain muscle substance.—There is marked atrophy of muscle, from which protein, potassium and magnesium are lost. In this way the total potassium in the body is greatly reduced. Waterlow and Mendes (1957) analysed samples of muscle obtained by biopsy and found the N content reduced by one-third.

The possible site of the biochemical lesion.—Waterlow (1961) has made a study of the enzyme systems present in the liver, using microchemical methods on biopsy material. He found that most of the respiratory enzyme systems were well maintained even in livers severely damaged. However, the build-up of inorganic phosphates into organic compounds was reduced. These and other results suggest an impairment of phosphorylation in the tissues. This elegant work may lead to fresh understanding of the chemical pathology.

Clinical features

A full account will be found in an excellent monograph by Trowell *et al.* (1954), and in an article by Hansen (1961).

Failure to grow is a constant and essential feature of the disease. The child's weight is usually much below standard for his age, but real weight may be masked by œdema. The muscles are always wasted and this is particularly noticeable around the chest ; the wasting of the legs and around the hips is frequently concealed by œdema. If the disease has resulted from a dietary restriction of both calories and protein, muscle wasting and an almost complete lack of subcutaneous fat is the most striking feature, but the feet are œdematous (' marasmic kwashiorkor '). Subcutaneous fat is often plentiful in children whose diets have provided ample calories but little protein. The child is often apathetic and this is a most serious prognostic feature. A return from apathy to irritability is a sign of successful initial treatment. The hair is nearly always affected in African children ; in Asiatics the changes are less frequent and less marked. There is an alteration in texture. The hair becomes fine, straight and soft, it loses its curl and lustre and is often sparse. The hair of African children may show a variety of pigmentary changes. Shades range from brownish-black and brown to a pale greyish-brown or even a straw colour. The extent of these changes in the hair is not necessarily an indication of the severity of the disease. Children who have been unwell for a long time but never seriously ill, may show them most markedly. Alterations in the skin are often present, especially in severe cases. These include pigmentation, depigmentation, desquamation and ulceration. The legs, buttocks and perineal areas are most frequently involved, but any region may be affected. This is in contrast to pellagra in which the dermatosis occurs mainly on the exposed surfaces. The skin lesions may be determined in part by associated vitamin deficiencies as described and discussed in Chapter 37. The liver may be greatly enlarged and extend down to the umbilicus. Anorexia and vomiting occur and there is often a distressing diarrhœa, with the passage of stools containing much undigested food. This feature may be secondary to the failure of the pancreas to secrete digestive juices, especially lipase. Important losses of potassium may result from the diarrhœa. There is nearly always some anæmia, but it is not usually very severe. Both the degree of anæmia and its nature are largely determined by associated infections and other dietary deficiencies.

Plate XV shows two typical patients.

Prognosis

Kwashiorkor is often a severe malady with a fatal termination, but it exists in a great variety of forms and may be so mild as to escape attention ; in such cases complete recovery is the rule. The name ‘ pre-kwashiorkor ’ has been suggested for the state of subclinical protein deficiency in children in which a failure in growth, a reduction in the serum albumin and an increased liability to diarrhœa and respiratory infections are the salient clinical features. There is good reason to believe that pre-kwashiorkor is extremely common in regions where the fully developed syndrome is found. But even mild degrees of fatty degeneration of the liver which heal with slow absorption of the fat, may leave a liver peculiarly susceptible to infections and other poisons. This combination of factors may lead to cirrhosis of the liver in late adolescence or early adult life—a condition which is common in many parts of the tropics (Chapter 39). Many children who suffer from the disease pass through their formative years with their physical and mental faculties partially impaired by their inadequate diet. The importance of this in the educational and physical development of Africans is not yet fully appreciated.

Differential diagnosis

A variety of diseases may be confused with kwashiorkor. Chronic dysentery, abdominal tuberculosis, cœliac disease, fibrocystic disease of the pancreas and nephritis are diseases which have clinical features in common with kwashiorkor. The age of onset, the dietary history and the response to protein therapy should help to distinguish them and, except in unusual cases, there should be little difficulty in differential diagnosis. It must be remembered, however, that kwashiorkor is often associated with other diseases.

The distinction from subnutrition and marasmus may be important.

Where there is a severe deficiency of calories as well as protein, a marked loss of weight is the presenting symptom. The obvious loss of subcutaneous fat without the classical changes in the hair and skin and with absent or minimal œdema suggests the diagnosis of marasmus. It should be realised, however, that borderline cases which have the features of both kwashiorkor and marasmus are not uncommon.

Infantile pellagra has been much confused with kwashiorkor in the past. The skin lesions in all types of pellagra are photo-sensitive, and unless the lesions are found on surfaces exposed to sunlight it is unwise to diagnose pellagra.

Hookworm infestation with anæmia and œdema may resemble kwashiorkor in many respects.

Prevention

This obviously depends upon eliminating the ætiological factors. Education in nutrition, the introduction of improved farming methods, including irrigation, and the development of food industries whereby protective foods may be made available in large towns at a reasonable cost to the consumer, are all important. In each country careful thought must be given to the provision of protein-rich foods made from local crops which are suitable both for infant feeding and for supplementing diets low in protein.

Such local research has been supported on a world-wide basis since 1957 by a generous grant made by the Rockefeller Foundation. This grant is administered by the Committee on Protein Malnutrition of the Food and Nutrition Board of the United States. Its research programme is concerned with the identification, production and utilisation of locally grown protein-rich foods of both vegetable and animal origin. A full report of the work carried out under these auspices was published recently (National Academy of Sciences, 1961).

Concentrates of vegetable protein made from oil-seed cakes, when combined with easily digestible sugars or cereal flours, have been found to be satisfactory substitutes for milk in the diet of infants. Flours made from pulses, suitably prepared to eliminate antimetabolites or toxic factors, can also improve the biological value of such mixtures. By mixing one vegetable product with another, deficiencies of amino acids in single proteins can be made good. For instance, sesame flour, which has a low content of lysine but ample amounts of methionine and tryptophan, can be blended with bean flour, which is rich in lysine, to make a mixture of high biological value. Most of the edible pulses have a high lysine content and so make good supplements to cereals such as wheat, sorghum and the millets.

Even small amounts of foods of animal origin such as dried milk or concentrates of fish protein, which are not readily available and are expensive in countries where kwashiorkor is prevalent, are of great value when mixed with high-protein vegetable foods. A mixture of one part of dried skimmed milk with three parts of groundnut flour, or one part of casein mixed with ten parts of groundnut flour, is as effective in the prevention and treatment of kwashiorkor as dried skimmed milk alone. The first is prepared by Cow & Gate in Nigeria and marketed as Arlac. The basic research which made the production of this product possible and established its nutritional and therapeutic value was carried out by the Nutrition Unit of the Nigerian Federal Ministry of Health and the Northern Nigerian Ministries of Health and of Trade and Industry. The second product, called Amama, is prepared and marketed in several African countries by Glaxo. The United Nations agencies, WHO, FAO and UNICEF, advised by a panel of nutritionists drawn from different parts of the world (the Protein Advisory Group), have assisted many countries to develop the local production of protein-rich foods suitable for the prevention and treatment of kwashiorkor. Examples are Saridele prepared from soya beans and sesame in Indonesia, fish-flour and sorghum in Senegal, and a mixture of cotton-seed flour with maize and sorghum in Central America (Incaparina : the name is derived from the initials of the Institute of Nutrition for Central America and Panama). Another very satisfactory but more expensive product has been prepared on a commercial scale in England from soya beans and chickpeas (*Cicer arietinum*), to which are added small amounts of methionine and vitamin B_{12}.

Concerted action by research units and foundations, government departments, international agencies and commercial interests, for promoting the production of such protein-rich foods, coupled with the nutritional education of all classes of the populations of underdeveloped countries, is essential if this world-wide cause of morbidity and mortality is to be eliminated.

Treatment

General.—A diet which provides sufficient calories and adequate amounts of easily digestible protein of good biological value, together with sufficient minerals and vitamins, is essential. Dried skimmed milk is the most useful form of protein for hospital patients and should always be used in treating serious cases in the early stages. If dried skimmed milk is not available or the cost of maintaining the supply of milk becomes prohibitive, protein-rich preparations such as one of those described above should be used as these have been shown to be effective substitutes for milk for such patients.

Very sick children need potassium to make good the deficiency caused by excessive losses in the stools. Vitamin A and ascorbic acid in suitable dosage should be given either as concentrates or in the form of a few drops of red palm oil and a teaspoonful of fresh orange juice. Therapeutic doses of iron should be administered.

The child's weight may fall during the first days of treatment due to loss of œdema fluid. The initiation of cure is indicated by increasing appetite and a gain in weight.

Diets for severe cases.—The following account is based on the experience of Trowell, Davies and Dean (1954) in Kampala, Uganda. De Maeyer (1954) in the Congo, Jelliffe (1959) and others have developed very similar procedures.

For the first day or two, if the child is unable to feed from a spoon, feeding by a Ryle's tube passed into the stomach through the nose may be necessary. A mixture of 150 g. of skimmed milk powder in 500 ml. of water is made up and given at 4-hourly intervals in sufficient amount to provide approximately 5 g. of protein for each kilogram of the ideal weight of a child of the same age. It is necessary to increase the diet slowly at first in order to avoid causing digestive disturbances, which may be fatal. On the second or third day it should be possible to start on a banana-milk or cereal-milk diet as follows :—

1. Take 400 g. of peeled sweet bananas, mash with a fork, spread out in a shallow dish and allow to stand for 6 to 8 hours.
2. Take 200 g. of dried milk, stir into a smooth paste with a little cold water, add hot water to a final volume of 500 ml. and heat to boiling. Allow to cool.
3. Mix the banana and the reconstituted milk thoroughly, if possible in an electric blender, adding up to 70 g. sugar.
4. Divide the mixture into six or eight equal amounts. Feed with a spoon.

This diet, which provides about 75 g. of protein and 1200 Cal., will lead to an improvement in appetite, digestion and strength. Bananas are the best vehicle for the milk protein, but if they are not available, semolina, rice or cereal flours may be tried instead. Any intolerance will be shown by diarrhœa—an indication for a reduction or change in the diet.

As the clinical condition improves the food consumption should be increased gradually until the child is eating a satisfactory diet of local pattern, including adequate amounts of easily digested protein-rich food. It is important that the mother should be taught how best to feed her child, using locally available foodstuffs. A satisfactory dietary protein level to maintain after cure has been attained is between 3 g. and 5 g./kg. of ideal weight.

POTASSIUM should be given to seriously ill patients. Infants may lose 1 to 4 g. of potassium chloride (13 to 52 mEq. K) in the stools in one day if there is severe diarrhœa. The effect of the resulting potassium depletion on the myocardium may cause sudden death. Potassium should be given by mouth as a routine to all infants admitted with kwashiorkor. On the first day the child receives 3 g. of KCl. (39 mEq. K) which can be added to the daily ration of reconstituted skimmed milk. This is given for a few days. Alternatively, potassium may be given in the following prescription :—

℞ Pot. acetate . .	1 g.
Pot. citrate , ,	1 g.
Pot. bicarbonate .	1 g.
Water to . ,	8 ml.

Dose.—One teaspoonful mixed with orange juice or glucose to be added to three feeds each day. There is little or no danger of potassium intoxication when this mixture is given by mouth in the dose recommended.

Parenteral therapy.—Protein hydrolysates, plasma and blood suggest themselves as agents suitable for parenteral treatment of protein deficiency. Conflicting claims for their value have been reported. It is a common experience that children with kwashiorkor, especially when œdematous, tolerate intravenous infusions poorly. Most physicians seldom employ parenteral therapy.

Vitamins.—The diets in patients with kwashiorkor are usually unsatisfactory and vitamin therapy has been used extensively. However, several writers have considered that vitamin therapy is of little value or even harmful. Perhaps an excess of one or two vitamins may further disturb an already deranged metabolism. Therapeutic diets based on skimmed milk and plant proteins are unlikely to be seriously lacking in any of the B group of vitamins and only in exceptional circumstances should it be necessary to prescribe them. Such diets are more likely to be deficient in vitamin A and ascorbic acid. If fish-liver oil preparations and fruit juices are not available or cannot be tolerated, then it may be desirable to give synthetic preparations of these two vitamins. Large doses should be avoided, 400 i.u. of vitamin A and 20 mg. ascorbic acid being sufficient. The importance of vitamin B_{12} as an ' animal protein factor ' is still undetermined (p. 240). Many physicians give 10 to 20 μg. of vitamin B_{12} daily parenterally, but there appears to be no satisfactory evidence that this has any effect on the disease, except when a megaloblastic anæmia is present.

Lipotropic factors accelerate the mobilisation of fat in the livers of experimental animals consequent upon the ingestion of defective diets or as a result of poisoning with a variety of toxic agents. Choline, methionine and preparations of pig's stomach, all known lipotropic agents, have been tried in kwashiorkor. Most workers have found them valueless and their use cannot be recommended as part of routine treatment.

Infections and Infestations.—The treatment of these is important. Most children will need worming, but all anthelmintics are toxic and may be lethal to patients who are seriously ill. Treatment must be postponed until convalescence is fully established. If anæmia from hookworm is so severe as to endanger life, blood transfusions should be given and will probably restore the child's condition sufficiently to permit worming later. Iron deficiency anæmia is frequently present as a result of dietary deficiency, infections and infestations, and requires appropriate treatment (p. 465). Much more rarely a megaloblastic anæmia is present which responds excellently to folic acid (p. 246). Antimalarial drugs in both prophylactic and therapeutic doses are well tolerated. Bacterial infections require the appropriate treatment with antibiotics, which appear to be well tolerated and effective. Tuberculosis, if not too far advanced, responds well to streptomycin combined with other appropriate drugs.

CHAPTER 29

RICKETS

DEFINITION

RICKETS is a nutritional deficiency disease occurring in infancy and early childhood. It is caused by a deficiency of vitamin D leading to an insufficiency of calcium in the body. The absorption of calcium from the gut is impaired. The diet is also usually poor in absorbable calcium. Lack of calcium affects the nerves, muscles and especially bones, with characteristic rachitic deformities of the latter.

History and natural history

Although rickets was described in ancient times, it was not well known until the seventeenth century. The first clinical description in Great Britain was that of Daniel Whistler, an Oxford man who wrote his D.M. thesis on rickets in 1645. This was followed in 1650 by the better known description of Glisson, a Cambridge graduate and physician in London. Contemporary writers described the thick pall of smoke that began to overcast London in the seventeenth century. Industrial smoke and high tenement buildings together shut out the sunlight and, as industrial cities grew, so rickets spread. Sunlight provides the ultraviolet rays which facilitate the synthesis of vitamin D in the skin. Although rickets may occur in children living in the country, it is never widespread unless local custom confines them indoors. Prior to 1900—in many of the great industrial cities of the world—up to 75 per cent. of the children of the poorer classes were affected. Rickets came to be known as ' a disease of poverty and darkness.' Glasgow, Vienna and Lahore each acquired an unenviable reputation as homes of the disease. In Lahore, as in many other eastern cities, the purdah system often confined women and children in narrow courtyards where the sun seldom penetrated. Rickets has been characteristically a disease of the poor rather than the rich. Milk (providing calcium) and cream, butter and eggs, the only common foods providing a satisfactory dietary source of vitamin D, may be too expensive for poor urban families. Wealthier families, on the other hand, not only enjoy these foods but usually also have access to gardens in which the children may benefit from sunlight. If the diet of poor families consists predominantly of cereals the inhibitory effect of phytic acid in the cereals on the absorption of calcium may be rachitogenic (p. 158). A plentiful supply of cereals provides calories which may enable growth to take place faster than the skeleton can be properly formed if calcium absorption is inadequate. Indeed it used to be a commonplace that the fat, flabby child, ' crammed with distressful bread,' which won the prize at the local baby show by virtue of being so much heavier than its competitors, was usually rachitic. The disease is liable to occur in premature, bottle-fed babies who grow rapidly.

The discovery of vitamin D in 1918 did not immediately resolve the confusion that existed about the ætiology of rickets. Lack of sunshine and lack of vitamin D each had their supporters. The classical researches of Dame Harriette Chick and her colleagues (1923) in Vienna after the First World War established the importance of both of these factors and explained for the first time the pathogenesis of the disease. Their report still remains the best account of rickets.

In the last 30 years rickets has virtually disappeared from Great Britain, as in many other countries. Indeed it has now become a rare disease. The reasons for this are manifold. Perhaps of first importance is the general recognition of the simple but sometimes forgotten truth, that milk is good for children. The various schemes which have resulted in a satisfactory supply of milk for the great majority of British children are probably the most important single factor that has brought about the abolition of rickets, even in the still-surviving industrial slums.

However, this should not belittle the additional contribution made by the clearance of slums and the building of new housing estates where sunshine can reach every home. The efforts of the Smoke Abatement Society have also contributed by decreasing both domestic and industrial smoke. The organised distribution of cod-liver oil has played an important role in ensuring protection against rickets. Better education in mothercraft is still needed to encourage proper use of this cheap and wise prophylactic measure.

The remarkable fall in the incidence of rickets is thus attributable to a variety of measures, many of which are now part of the established social policies of civilized countries. It would be rash to suggest that any one of these measures is now redundant.

The last sentence was first written many years ago. That it is still sensible is illustrated by a recent paper. Dunnigan and his colleagues (1962) report seven cases of clinical rickets in Pakistani children aged 7 to 14 years living in Glasgow. In twenty-eight members of their families there was biochemical or radiological evidence of vitamin D deficiency, but no clinical signs. These children developed rickets from a combination of well-known causes—Glasgow's pall of smoke and inadequate houses, Muslim seclusion of women and poor oriental diets. It is interesting that none of the young children in these families were affected. This apparently was because Pakistanis make full use of the cod-liver oil and other Welfare Food Services provided in Scotland for infants.

In children and also in adults rickets may arise secondarily to disease of the alimentary canal or the kidney (Chapter 30).

Morbid anatomy

The morbid histological changes in the bones in active human rickets are essentially the same as those in experimental animals as described on page 203. Although there are no characteristic microscopic changes in the nerves and muscles, they are none the less affected by the deficiency of calcium.

Chemical pathology

With the deficiency of calcium in the body, the calcium in the blood serum tends to fall from its normal level of about 10 mg./100 ml. It may fall as low as 5 mg. or even less, which usually causes tetany (see below). More commonly the serum inorganic phosphorus falls from the normal level of about 3·5 mg./100 ml. to 3 mg. or less. This is thought to be due to the activity of the parathyroid glands which respond to a slight reduction in serum calcium by increasing the excretion of phosphorus in the urine, with consequent reduction in the level of inorganic phosphorus in the blood. A low serum phosphorus and normal serum calcium in rickets suggests a full parathyroid response which is likely to result in considerable rarefaction of bone. A low serum calcium and normal phosphorus, on the other hand, suggests a failure on the part of the parathyroid glands to respond. In such cases the main feature may be tetany, without much change in the bones.

It should be emphasised that clinical rickets may occur when the levels of calcium and phosphorus in the serum are still within normal limits. A more constant change is an increase in serum alkaline phosphatase. This enzyme is probably formed by the large number of osteoblasts which accumulate in the osteoid tissue at the growing points of the bones. These cells, unable to make bone without a sufficient supply of calcium, probably liberate into the circulation the excess of this enzyme which they cannot use. Alkaline phosphatase in serum or plasma is measured in King-Armstrong units ; the normal value in the first 3 years of life is up to 15 units. Even in early mild cases of rickets 30 to 40 units are quite frequently found. Such levels do not necessarily increase as the disease progresses so that the determination of alkaline phosphatase, though valuable in the diagnosis of rickets, gives no index of its severity.

The tetany that results from a reduction of ionised calcium in the blood is due to hyperexcitability of the neuromuscular conducting mechanism.

Clinical features

The infant with rickets has often received sufficient calories and may appear well nourished. But he is restless, fretful and pale, with flabby and toneless muscles which allow the limbs to assume unnatural postures (‘ acrobat*i*c rickets ’). Excessive sweating of the head is common. The abdomen is distended as a result of the flabby abdominal muscles, the atony of the intestinal musculature and the intestinal fermentation that may arise from excessive carbohydrates in the diet. Gastrointestinal upsets with diarrhœa are common. The infant is prone to respiratory infections, although these are probably due not so much to the disease itself as to the other unhealthy aspects of the environment. Development is delayed so that the teeth often erupt late and there is failure to sit up, stand, crawl and walk at the normal ages. Plate XVI shows a typical rachitic child.

The bony changes are the most characteristic and easily identifiable signs of rickets. There is extension and widening of the epiphyses at the growing points, where cartilage meets bone. The earliest bony lesion is often *craniotabes*—small round unossified areas in the membranous bones of the skull, yielding to the pressure of the finger, with a crackling feeling, like parchment. Another early sign is enlargement of the epiphyses at the lower end of the radius and at the costochondral junctions of the ribs, the latter producing the clinical sign known as ‘ beading ’ of the ribs or ‘ rickety rosary.’ Craniotabes usually disappears after six months, but later there may be ‘ bossing ’ of the frontal and parietal bones and delayed closure of the anterior fontanelle. Later too, there may be deformities of the chest such as undue prominence of the sternum (‘ pigeon chest ’) and ‘ Harrison’s sulcus ’—the latter apparently caused by the sucking in of the softened ribs on inspiration during whooping cough, or other respiratory infections to which rachitic children are prone.

If rickets continues into the second year of life, these signs may persist or be magnified. Deformities such as kyphosis of the spine develop as a result of the new gravitational and muscular strains, caused by sitting up and crawling. At the same time there may be enlargement of the lower ends of the femur, tibia and fibula. When the rachitic child begins to walk, deformities of the shafts of the leg bones develop, so that ‘ knock knees ’ or ‘ bow legs ’ are added to the clinical picture. The spinal kyphosis is often replaced by lordosis. Pelvic deformities may follow and lead many years later to serious difficulties at childbirth in women who have suffered from rickets in childhood.

When there is a reduction in the level of ionised serum calcium infantile tetany may result, with spasm of the hands and feet and of the vocal cords. The latter causes a high-pitched, distressing cry and great difficulty in breathing. In bygone days—when florid rickets was common—tetany was sometimes associated with alarming general convulsions.

Diagnosis

In a fully developed case this is easy. But in countries where the disease is now rare, there is an increasing likelihood that mild cases will be missed. A flabby baby towards the end of its first year, unable to pull itself up, fretful and easily irritated, with too few teeth showing and liable to profuse sweats, should always be suspected of rickets. The diagnosis may be supported by the dietary history. Early evidence of rickets may be overlooked in a child ill with bronchopneumonia or diarrhœa. If there is any doubt or suspicion, radiological examination of the wrist will show characteristic changes at the epiphyses ; the outline of the joint is blurred and hazy, and the epiphyseal line becomes broadened. Later, in older children, as a result of decalcification of the metaphysis and the effects of movements and stresses the classical concave ' saucer ' deformity is clearly shown radiographically. The opinion of an experienced radiologist may be needed to distinguish the picture from that of infantile scurvy. A raised level of serum alkaline phosphatase gives the best objective support to the initial clinical diagnosis.

It is sometimes necessary to distinguish rickets from other rare disorders involving the bones, such as congenital syphilis, achondroplasia and osteogenesis imperfecta. Radiological examination of the bones is helpful in differentiating these disorders.

Treatment

The two essentials of treatment are the provision of a supplement of vitamin D and an ample intake of calcium. A therapeutic dose of vitamin D will vary from 1000 to 5000 i.u. daily, depending on the severity of the disease. In contrast, the prophylactic dose is 400 i.u. or less daily. A British Pharmacopœial (B.P.) preparation of cod-liver oil contains not less than 300 i.u. per teaspoonful (about 4 ml.). For severe cases needing 5000 i.u. daily, synthetic calciferol is useful because the amount of cod-liver oil required to provide this dose may be too bulky, although usually relished by infants and young children. For such patients the B.P. concentrated solution of vitamin D is satisfactory. About 2000 i.u. of vitamin D are present in 0·2 ml. (2 to 3 drops) of this preparation. In times of social upheaval, such as may be occasioned by war, floods or pestilence, where an infant or young child may be seen once by an emergency medical service and perhaps not again for months, a single massive dose of vitamin D, *e.g.* 150,000 i.u., can be given by mouth with reasonable safety and curative effects. The single dose can be given by intramuscular injection but this has no proved advantage over the oral route. The daily administration of small doses is the method recommended for normal practice, because of the danger of overdosage (p. 205).

In addition to vitamin D, rachitic infants and children require an ample supply of calcium, the best source of which is milk. At least one pint (about ½ *l.*) should be taken daily by a young child with mild rickets. For a severe case a supplement of calcium gluconate should also be given orally. The diet after weaning can include with advantage an egg daily and some butter. An adequate intake of iron and ascorbic acid is also needed.

Vitamin D and diet are not the whole solution to the treatment of rickets. An attempt must be made to improve the hygienic environment of the child. This often requires the tactful education of the mother in better feeding practices and general care. Unnecessary clothing should be removed and, if the child was previously confined indoors, he should be allowed out as much as possible to enjoy the sunshine.

The earliest evidence of healing in rickets is provided by radiological examination of the growing ends of the bones. The levels of calcium and phosphorus in the serum provide an inconstant and unreliable guide. The serum alkaline phosphatase does not usually diminish for several weeks or months after adequate treatment is initiated ; the therapeutic dose of vitamin D should be continued so long as the phosphatase level remains elevated ; thereafter it may gradually be reduced to the prophylactic dose of 400 i.u. daily.

Occasionally cases of rickets are encountered that are resistant to ordinary therapeutic doses of vitamin D. The disease persists into late childhood (' late rickets ') or even adult life, producing the clinical appearance of osteomalacia, unless adequately treated. The cause of this resistance is not understood, though perhaps it is due to excessive loss of phosphates in the urine. A similar state may sometimes arise as a conditioned deficiency resulting from malabsorption or renal failure. Whatever the cause, treatment consists in giving large doses of vitamin D by mouth in the form of calciferol in oil, together with calcium salts, *e.g.* calcium gluconate in pill or powder form, 5 g. three times daily. The initial dose of calciferol may be 150,000 i.u. daily or even more, but it should be reduced at the first suspicion of toxic symptoms (p. 205).

Prognosis

Rickets is not a fatal disease *per se*, but the untreated rachitic child is always a weakling owing to the risk of infections, notably bronchopneumonia. For some unknown reason the skeletal changes usually tend to heal spontaneously as the child gets older. The bony deformities—if mild in degree—usually right themselves as growth proceeds, but in severe cases pigeon chest, contracted pelvis, knock knees or bow legs may persist. With early and sufficient treatment these changes are entirely avoided.

Prophylaxis

The provision of adequate milk for children, the clearing of industrial city slums, the building of new housing estates and the attack on the smoke nuisance are basic prophylactic measures which must be continued at all costs. If a young child can have one pint of cow's milk, an egg and some butter daily, and has free access to a garden in which he can run about in the sun, the administration of a supplement of vitamin D is not essential for his future health. Nevertheless practical experience shows that the majority of children who do not enjoy these advantages regularly, or who live in a climate where sunshine is scanty, benefit by receiving a daily supplement of about 400 i.u. of vitamin D, preferably in the form of some natural source such as cod-liver oil, which also provides useful amounts of vitamin A. In some countries it is necessary to remember that fish oils may be adulterated by the addition of vegetable oils ; the label on the bottle should clearly state the vitamin D content of the oil, as attested by some reliable agency.

Before deciding on the prophylactic dose of cod-liver oil or other fish oil, it is necessary to consider how much vitamin D the infant is getting from other sources. Thus, if he is being brought up on a preparation of dried milk ' fortified ' with vitamin D (*e.g.* British National Dried Milk which contains 100 i.u. per oz. of powder) the supplement of cod-liver oil should be small. Furthermore, it should be remembered that some proprietary cereal foods for infants are ' fortified ' by the manufacturers with vitamin D.

All brands of British margarine are fortified with vitamin D and contain about twice as much vitamin D as butter. This may help to secure good calcification of the bones during the growth of older children.

Not only is there no advantage in giving infants and young children more than 400 i.u. of vitamin D daily *from all sources* for prophylactic purposes, but there is a distinct possibility that higher doses given over a long period may have harmful effects. The potential dangers of over-dosage with vitamin D have been emphasised by the discovery of infantile hypercalcæmia in Great Britain (p. 166). The problem of achieving a satisfactory prophylactic dose, neither too small nor too large, when the child may be receiving vitamin D from several different sources—cod-liver oil, ' fortified ' dried milk and a ' fortified ' proprietary cereal—has been reviewed by a committee under the chairmanship of Lord Cohen (1957).

It should be noted, however, that the prophylactic dose of vitamin D for premature infants should be twice that for full-term infants and the supplement should be given earlier, *i.e.* starting about the fourth week after birth. There has been divergence of view among pædiatricians in the past about the length of time that the prophylactic administration of vitamin D should be continued. Obviously such features as the social and economic status of the parents and the climate in which the family lives are matters of importance. It seems reasonable to suggest that in temperate climates at least, a daily intake of about 400 i.u. should be continued summer and winter for the first five years of life, in accordance with the recommendations of Lord Cohen's committee (*loc. cit*).

CHAPTER 30

OSTEOMALACIA AND OSTEOPOROSIS

THESE are two chronic diseases of the skeleton. Although they have a similar effect on the mechanical function of bone because they weaken the parts affected, the pathological and chemical changes and treatment are different. Hence it is customary in textbooks to describe each disease separately. For reasons given below it is possible that the distinction may not be so sharp since recent evidence suggests that calcium deficiency may be of ætiological and therapeutic importance in both diseases.

Osteomalacia, which means softening of bone, is due to a deficiency of calcium or vitamin D, or both, which results in a failure to lay down calcium and other minerals in the organic matrix of bone. Hence the ratio of calcium phosphate to matrix is reduced.

Osteoporosis, which is an atrophy of bone, is believed to be due to defective formation of bone matrix which leads to a reduction in the total quantity of bone. In contrast to osteomalacia the ratio of calcium phosphate to matrix is normal. Osteoporosis may be a generalised disease of the whole skeleton or a localised disorder affecting only portions of individual bones. It may arise from a variety of causes which will be discussed below. It is common in old people in all countries. Senile osteoporosis is the cause of much suffering. The treatment of the fractures which are so frequent in the elderly, and arise from the reduced strength of the bones has always been an important medical problem. Many hospital beds are occupied by elderly people with fractures who require much attention from both nursing and medical personnel.

Before discussing these diseases in detail it is important to remember that the living skeleton differs greatly from the specimens which are familiar objects in anatomy museums. In life the bones are not dead supporting scaffolds but are living tissues with metabolic activity continuing all the time. Organic matter contributes just over half the weight of the skeleton. The relative weight of the skeleton varies greatly in individuals ; a normal figure being 15 per cent. of the body weight or 10 kg. in a 65 kg. man. Of this 10 kg. approximately 2 kg. is protein and 1·5 kg. calcium. These amounts are large in comparison with the daily losses of protein and calcium that might be expected in a person on an inadequate diet or with a disturbance of alimentary absorption or with a metabolic disorder. In consequence generalised bone disease develops slowly ; months or often years may elapse before obvious clinical or radiological signs appear.

OSTEOMALACIA

Ætiology

Osteomalacia is the adult counterpart of rickets. The dietary and environmental circumstances necessary to produce it are so grossly abnormal that fortunately it is a rare disease, at least in its fully developed form. This is found in women who live on very poor cereal diets devoid of milk, who are kept indoors all day and seldom see the sun, and who by repeated pregnancies become depleted of calcium. The disease was common in Northern China, parts of North India and Pakistan, Kashmir and Japan. Hunger-osteomalacia occurred in Vienna from 1918 to 1920, arising out of the misery and poverty that followed the final collapse of the Hapsburg Empire. Nowadays the disease due to malnutrition is rarely reported from Europe. Osteomalacia occurs in Europe and North America usually secondary to some form of the malabsorption syndrome (p. 508).

Pathology

The changes in the blood are essentially the same as those in rickets. The progressive decalcification of the bones leads to the replacement of bony substance with soft osteoid tissue. This process goes on all over the skeleton, but the effects are greatest in the spine, pelvis and lower limbs.

Clinical features

The following account is based on that given by Dr Dagmar Wilson (1929) who had experience of the disease in Kashmir. Dalyell and Chick's (1921) description of the disease in Vienna is similar.

1. The onset often coincides with the first pregnancy, a remission occurring after delivery ; but symptoms return in more severe degree with each succeeding pregnancy.

2. The gait is uneven on a slightly wide base. This is due to pain in the tarsal and metatarsal bones. The patient shows a tendency to swing the leg outwards before putting the foot to the ground. The pelvis from behind may appear flattened, wider than normal and slightly tilted.

3. Pain is usually present and ranges from a dull ache to severe pain. Common sites are over the sacrum and lower lumbar vertebræ, or the bones of the pelvis and legs. Pain may also be severe in the ribs.

4. Tenderness on pressure is common at many bone prominences. It is often especially marked over the tibia.

5. Tetany is often manifested by carpopedal spasm and facial twitching. The knee jerks may be exaggerated.

6. Spontaneous fractures occasionally occur, independent of the pseudo-fractures described below.

7. Some degree of anæmia is almost always present, doubtless due less to lack of iron than to deficiency of other dietary factors, since menstrual loss is usually scanty.

Diagnosis

When the characteristic deformities are present this is easy, but in early cases it may be difficult. The early symptoms probably cannot be distinguished from those present in osteoporosis and may also be mistaken for rheumatism.

Radiological examination of the bones in osteomalacia shows generalised rarefaction. In addition there may be bilateral, symmetrical pseudo-fractures (Looser's nodes) at points where arteries cross the bones. Common sites are: the axillary borders of the scapulæ, the pubic rami and the shafts of the femora on the medial side, below the hip joint. The radiological appearance of these nodes is that of a wedge-shaped piece of bone having been cut out with scissors. They are not true fractures, since the clear space of the wedge is found at autopsy to contain callus. This striking radiological picture is pathognomonic of osteomalacia. It has been referred to in the past by radiologists as 'Milkman's syndrome,' before its nutritional significance was recognised.

Treatment

This is essentially the same as for rickets. Large doses of vitamin D by mouth (*e.g.* 50,000 i.u. daily) may be necessary at first. Milk and eggs should be added to the diet, but under the conditions in which the disease arises in the East, this is often impracticable. Six grams of calcium lactate may be given as pills or a powder added to food three times daily. About one-fifth of the weight of calcium lactate is calcium, so this provides a daily dosage of 3½ g. of calcium. Contraction of the pelvis frequently necessitates Cæsarian section in pregnant women. Once deformities are established, they cannot be corrected either by diet or drugs but only by an orthopædic surgeon, for whom they present serious technical problems.

Prevention

This is difficult in oriental countries since osteomalacia has usually occurred in backward communities where the women are held in subjection. It is frequently associated with the purdah system. Free access to fresh air and sunshine and a fair share of the limited family supply of dairy produce, supplemented with fish-liver oil, will help to reduce the incidence. With improved education and better standards of living the disease is now rare in many Asiatic towns where formerly it was common.

SECONDARY RICKETS AND OSTEOMALACIA

The clinical picture of rickets or osteomalacia is occasionally seen as a result of other diseases which 'condition' the calcium deficiency. These diseases are of two kinds :—

1. **The malabsorption syndrome** (p. 508).—If the intestinal absorption of fat, and therefore of fat soluble vitamin D, is impaired, the body is

deprived of a sufficiency of this vitamin to promote the normal absorption of calcium. At the same time the unabsorbed fatty acids form insoluble soaps with the calcium, thus further inhibiting its absorption. In its childhood form (cœliac disease) this may cause ' late rickets.' In the adult secondary osteomalacia may result (Badenoch & Fourman, 1954). Treatment should include both calcium salts and vitamin D by mouth, in the doses recommended above for primary osteomalacia, preferably taken between meals so that undigested fatty acids do not interfere with their absorption. In addition the cause of the malabsorption must receive appropriate treatment.

2. **Renal disorders.**—In a variety of rare disorders of the kidneys, including that collector's piece, the *Franconi syndrome*, there is a disturbance of renal tubular function affecting the excretion of cations. Sodium and hydrogen ions are retained, resulting in acidosis, and there is increased excretion of calcium ions. Calcium is withdrawn from the skeleton and ' renal rickets ' follows in children and osteomalacia in adults. A discussion of these disorders is beyond the scope of this book. The reader can find details in an editorial (*Lancet*, 1961*a*), which has many references. Patients with renal rickets and osteomalacia may derive great benefit from treatment with calcium and vitamin D. Dosage may have to be large and 6 g. of calcium lactate three times a day, and 50,000 i.u. of vitamin D may be needed. The accompanying acidosis will also require treatment.

OSTEOPOROSIS

With the possible exception of Paget's disease, osteoporosis is the disease of bone most commonly encountered in clinical practice. It may be a localised or generalised disease.

Local osteoporosis.—This may arise as a result of inflammation or neoplasm of bone. The most common cause is immobilisation. Disuse removes the stresses and strains which stimulate the osteoblasts to lay down new bone, whilst the osteoclasts continue to remove calcium salts. This happens when movement is restricted by splinting, by inflammation or by pain, or when a patient is confined to bed. Extra provision of nutrients in the diet cannot prevent this process.

Generalised osteoporosis.—This occurs in a variety of diseases and is very common in old age. A full review of the subject has been given by Cooke (1955) who gives details of the pathological changes in the bones and the clinical features.

Ætiology.—Osteoporosis is a feature of many endocrine disorders. The parathyroid glands mobilise calcium from the bones and in hyperparathyroidism there is a general diffuse atrophy of bone and sometimes localised areas of intense demineralisation. The adrenal cortex and the thyroid gland both exert some control on bone structure. When these glands are overactive, as in Cushing's disease and Graves' disease, osteoporosis develops. In both these diseases there is an increased rate of protein catabolism; the osteoporosis probably arises because of a failure to maintain the protein matrix on which the minerals in the bone are laid down.

The gonadal hormones also assist in maintaining skeletal structure. In experimental animals prolonged treatment with both male and female sex hormones may lead to hyperossification, and castration sometimes leads to osteoporosis. In man defective bone growth and osteoporosis may be found in patients with primary gonadal insufficiency. The male sex hormones are well known to have an anabolic effect. In their absence or relative deficiency the protein matrix of bones may not be adequately maintained. The traces of androgens secreted by females may have a similar function.

The association between a normal endocrine balance and a normal skeletal structure is beyond dispute, but it should be remembered that endocrine imbalance may exist for a long time without detectable changes in the skeleton.

Albright and Reifenstein (1948) suggested that senile osteoporosis was an endocrine disorder and arose as a result of a failure of the sex hormones to maintain the protein matrix of the skeleton. The fact that osteoporosis is both more common and severe in elderly women than in old men could be explained by the earlier and more abrupt cessation of gonadal function at the menopause in women. Albright clearly demonstrated that the symptoms in senile osteoporosis can often be markedly relieved by hormonal therapy. Largely as a result of his writings senile osteoporosis has been widely accepted as being an endocrine disorder and not primarily related to dietary deficiency of minerals. The fundamental pathology was considered to be a failure to maintain the protein matrix, rather than a failure to provide calcium for its mineralisation. This view has now been challenged.

In Glasgow, Nordin (1961), and in London, Russell Frazer (Harrison *et al.*, 1961) have confirmed the findings of the Aberdeen workers, Owen *et al.* (1940) who showed that patients with osteoporosis given supplements of calcium went into strongly positive calcium balance. There is now much evidence to suggest that osteoporosis often arises as a result of a long period of negative calcium balance. This may be due in part to inadequate intake, in part to diminished alimentary absorption, and in some cases to an increased urinary excretion of calcium. The most convincing evidence to support their views is the demonstration, many times repeated, that if patients with senile osteoporosis are given large amounts of dietary calcium (2 to 3 g./day) the majority retain from 0·5 to 1 g. calcium daily. Healthy controls, when given such high calcium diets, retain little or none of the extra mineral. Urinary output of calcium is very variable in patients with osteoporosis. In some patients it is high, even when they are on diets low in calcium; in others it may be comparatively low, even on a high intake. This contrasts with the handling of protein by osteoporotic patients. The excretion of urinary nitrogen is closely dependent on the intake of dietary protein.

If it is accepted that long-continued calcium deficiency is of ætiological importance in osteoporosis, it should be pointed out that the negative calcium balance could result from lack of dietary calcium, from an increased rate of bone resorption, or from an excessive loss of calcium in the urine or fæces.

Clinical features.—These are very variable and there may be none at all. X-ray examination of an old person with a fracture may reveal extensive generalised osteoporosis, yet there may have been no previous clinical evidence of disease. On the other hand, there may be much pain, which can be so severe as to be completely incapacitating. The pain is usually in the back and radiates round the trunk into the buttocks and down the legs. It is made worse by movements or jarring and sometimes by coughing or straining at stool. The most common clinical finding is a shortening of the trunk leading to a hump back. This can be shown by radiology to be due to decalcification and subsequent deformity of the vertebræ. Although the symptoms suggest pressure on the roots of the spinal nerves and there is deformity of the vertebræ, compression of the cord does not occur.

The blood chemistry is unchanged and levels of calcium, phosphate and plasma proteins are normal.

Treatment.—It is essential to get the patient up and about as much as possible. If she has been bedridden, it will help to get her sitting in a chair. If there is much pain a light spinal brace may help. Whatever one's views about the ætiology of the disease, a good mixed diet is desirable. One pint of milk, which will provide 20 g. of protein and 700 mg. of calcium, should be given daily. Additional calcium should be given. Nordin has used a dose of 6 g./day of calcium glycerophosphate (equivalent to 1100 mg. of calcium) and found improvement in the symptoms, especially relief of backache, in the majority of the patients treated. Improvement is often slow and may only occur after many months. Small doses of vitamin D may help.

Hormonal therapy has undoubtedly benefited many patients by relieving their pain. Cooke (1955) recommends testosterone propionate 10 to 20 mg. daily by injection or methyl testosterone, 30 mg. daily by mouth. This should be combined with a female hormone such as œstradiol benzoate, 2 mg. daily by injection or dienœstrol, 1 mg. daily by mouth. There are satisfactory proprietary mixtures of male and female sex hormones. Large doses are not needed and may have undesirable side-effects.

Although there is satisfactory evidence that both hormonal therapy and additional calcium will often relieve the symptoms and make the patient more comfortable, radiological examination fails to show that either form of therapy has been responsible for laying down significant amounts of new bone. Treatment can arrest the disease but seldom leads to cure.

Prevention.—As senile osteoporosis probably often begins around the age of 50 and may take 30 years or more to develop, its prevention is obviously a formidable task. An active life and a well-balanced diet are certainly the best preventive measures. It is most important that middle-aged and elderly persons with chronic diseases do not allow their ill-health to immobilise them. All such patients must be encouraged to take exercise as much as their disability permits.

A programme of hormonal prophylaxis which would have to be continued over decades in apparently healthy people is impractical. A good mixed diet for all middle-aged and elderly people is indicated. It should contain sufficient calories to meet the needs for their daily activities, but no excess. Protein and calcium are probably needed in amounts as great as for young adults (Chapter 15). If a pint of milk is drunk daily these requirements will be largely met. Although scientific evidence from field trials is lacking, it would seem probable that milk is as valuable in maintaining old bones as it has been proved to be in making new bones in the growing child.

Chapter 31

SCURVY

SCURVY is a nutritional disease which results from prolonged subsistence on diets practically devoid of fresh fruit and vegetables. Its characteristic features are due to lack of ascorbic acid, causing a disturbance in the structure of extracellular connective tissue. They include swollen, bleeding gums and hæmorrhages into the skin and elsewhere in the body.

History and epidemiology

Scurvy was not clearly recognised by Greek, Roman or mediæval physicians. In 1453 Constantinople was sacked by the Turks, so that Venice lost naval control of the Eastern Mediterranean, and the overland trade route between Europe and Asia was blocked. This disaster for Christian merchant adventurers stimulated the Portuguese to find a sea route to India. In 1497 Vasco de Gama sailed round the Cape of Good Hope and established a trading centre on the Malabar coast. Scurvy broke out among his crew on the voyage and a hundred out of his hundred and sixty men died. For the next 300 years scurvy was a major factor determining the success or failure of all sea ventures, whether undertaken for purposes of war, trade or exploration. As early as 1535 the French explorer Jacques Cartier, whose crew was severely affected in Newfoundland, discovered that the juice of the leaves of a certain tree had remarkable antiscorbutic properties. Hakluyt's account of this discovery, as recorded in his *Principal Navigators* (1600), is reproduced as an Appendix to this chapter.

Later Canadian explorers, suffering from scurvy, attempted to identify the curative Ameda tree without success, probably because the Indians by then were less communicative. The tragedy was that as they died of the disease the tree was probably standing right beside them ; for as Lind suggested, it was probably the spruce fir. The value of a decoction of spruce or pine needles as an antiscorbutic remedy was well known to the Swedes at least as early as the sixteenth century, and subsequently used by the Russians in their repeated attempts to find an Arctic sea-route to the Pacific. Curiously the antiscorbutic value of pine needles was rediscovered in the U.S.S.R. in 1943.

The subsequent history of scurvy is of great interest. Many writers showed that the disease could be cured by a variety of fresh fruits and vegetables, but medical learning was so constricted by Galen's classical pathology of ' humours ' that the conception of a deficiency disease was not realised till long after. In 1753 Lind, a Scots naval surgeon, published

A Treatise of the Scurvy, in which he showed not only that the disease could be cured by fresh oranges and lemons, but also that it could be prevented by adequate dietary and other hygienic measures. His own account of the first controlled therapeutic trial ever undertaken is as follows :—

> " On the 20th of May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for sick in the fore-hold ; and had one diet common to all. . . . Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutta of *elixir vitriol* three times a-day, upon an empty stomach ; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach ; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid . . . were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with greediness, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-surgeon, made of garlic, mustard-seed, *rad. raphan.*, balsam of Peru, and gum myrrh ; using for common drink, barley-water well acidulated with tamarinds. . . .
>
> The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons ; one of those who had taken them, being at the end of six days fit for duty. . . . The other was the best recovered of any in his condition ; and being now deemed pretty well, was appointed nurse to the rest of the sick. . . ." (Lind, 1753).

Lind was aware that an adequate supply of fresh vegetables or a suitable fruit juice could prevent the occurrence of scurvy. He states that abstinence from them is " the occasional (*i.e.* apparent) cause of the evil " but other factors such as exposure to cold and wet, drunkenness, putrid air and overcrowding below decks were ' predisposing causes.' Such factors, often to-day loosely called ' stress,' are now known to have important effects on ascorbic acid metabolism as already discussed in Chapter 14.

Captain James Cook was the first person to demonstrate that a long voyage could be undertaken without the crew developing scurvy. In his voyage round the world from 1772 to 1775 in which he explored Australia and New Zealand, none of his men developed the disease, thanks to the care with which he seized every opportunity to provide them with fresh vegetables and fruit (including oranges and lemons) whenever they touched land. But it was not until 1795, 42 years after the publication of Lind's treatise, that his pupil Sir Gilbert Blane persuaded the Lords of the Admiralty to put his precepts into practice and thus immediately abolished scurvy from the Royal Navy. This was at the beginning of the Napoleonic wars when Great Britain's command of the sea was of paramount importance to her. The application of Lind's teaching doubled the fighting force of the Navy at sea without adding a penny to the naval estimates. For a further 50 years however, the disease lingered on in the merchant navies of the world. The long interval between the discovery of the new knowledge and its application to the benefit of the health of sailors makes a sad story in human history.

Although scurvy ceased to be an important disease of sailors, it continued to afflict the garrisons and civil populations of besieged towns and those confined to prisons. It also developed in another section of the community; the knowledge of the chemistry of foods obtained in the nineteenth century enabled a variety of preserved and artificial milks to be manufactured. These provided an adequate substitute for the protein, fat and carbohydrate in human milk and so removed the wet nurses from our society. But these substitutes for human milk contained little or no ascorbic acid, so scurvy in infants became an important disease. The hey-day of infantile scurvy was in the last 20 years of the nineteenth century. It still occurs as a result of maternal neglect, poverty, or, occasionally, of excessive maternal care. Mothers have been known to boil their infants' orange juice with the object of sterilising it; this, of course, destroys the ascorbic acid it contains. At a later date, cases of scurvy used to arise among adult patients treated for peptic ulcer by severe and prolonged dietary restriction. When knowledge of the importance of the vitamin was established early in this century scurvy soon became a rare disease in Great Britain; to-day few physicians have much personal experience of it. Nevertheless sporadic cases of the disease continue to arise, though chiefly now at the other extreme of age, amongst old people. There are now in our cities an increasing number of old people who live alone and have neither the opportunity nor the aptitude to feed themselves properly, so that they sometimes develop scurvy. The social problem of ensuring the satisfactory nutrition of old and solitary people has yet to be solved.

Scurvy is usually a rare disease amongst rural people; in the countryside there are nearly always sufficient vegetables to prevent the disease. A notable exception was the Irish potato famine of 1845-47, when blight destroyed the potato crop. Starvation and scurvy, accompanied by typhus and relapsing fever, depopulated the country, as described in Chapter 53.

Scurvy sometimes occurs in semi-desert parts of the world in times of drought, as in parts of India for instance, after a failure of the monsoon rains. A scholarly account of the history of scurvy in France has been given by Claudien (1958).

Ætiology

Scurvy results from the prolonged consumption of a diet devoid of fresh fruit and vegetables. The principal deficiency in such a diet is the lack of ascorbic acid, and this deficiency is responsible for the characteristic features of the disease. Nevertheless such diets are likely to be deficient also in other nutrients such as iron, vitamin A and sometimes protein. Thus although ascorbic acid will relieve the predominant signs of the disease, it does not always completely cure the patient. Further, although a diet may seem from the history to contain adequate amounts of ascorbic acid, it may in fact be scorbutic if practically all the vitamin has been destroyed in its cooking.

Another factor in the ætiology of scurvy may be the influence of ' stress ' as already discussed in Chapter 14. This may result in increased utilisation of ascorbic acid in the body.

Chemical pathology

The part played by ascorbic acid in maintaining the health of connective tissue is not understood in precise chemical terms, nor is there any easily detectable disorder of the chemistry of the body that can be used as an aid in the diagnosis of ascorbic acid deficiency. Although the administration of tyrosine by mouth to scorbutic infants results in an increased excretion of tyrosyl derivatives in the urine, this should not be used as a diagnostic test for scurvy, since it may be dangerous for the baby.

Morbid anatomy

Fatal cases of human scurvy have been so rare in the past 40 years that there have been few opportunities to study the morbid anatomy. However, from the earlier account of Aschoff and Koch (1919) and from the results of biopsy material in experimental ascorbic acid deficiency in man, there is good evidence that the essential histological changes in man are the same as those produced experimentally in guinea-pigs.

Lind himself remarked on the ' peculiar laxness ' of the tissues at autopsy. This is no doubt due to the lack of collagen in the connective tissues. The fibrous tissue of old scars may break down and recent wounds show no sign of healing. The gums are swollen, due partly to œdema in the lax tissues and partly to actual hypertrophy with an overgrowth of fibroblasts, lacking the collagen fibres that usually surround them. Any interstitial bleeding will, of course, intensify the swelling. In chronic cases the teeth may become loose and even fall out, through lack of the cement that binds them. A terminal infection often cuts short the course of infantile scurvy and adds to the pathological appearances.

Autopsy may reveal hæmorrhages, gross or microscopic, anywhere in the body, some of which may not have been suspected in life. They are ascribable to the lack of intercellular cement substance between the endothelial cells of the capillaries and to breakdown of the fibrous walls of small arteries.

Clinical features

The best clinical account of scurvy is that given by Lind who had greater experience of the disease than any modern physician and described his observations with the clarity and elegance characteristic of his age.

Lind said that the pathognomonic sign of the disease was the appearance of the gums and certainly the characteristic gingivitis often first suggests the diagnosis. The gums are swollen, particularly in the region of the papillæ between the teeth, sometimes producing the appearance of 'scurvy buds.' These may be so extensive that they project beyond the biting surface of the teeth and almost completely conceal them. The swollen gums are livid in colour and bleed on the slightest touch. There is always some infection; indeed this seems necessary for the production of the scorbutic gingival appearances since human volunteers suffering from ascorbic acid deficiency did not develop it if their gums were previously healthy. Associated with the infection there is a strikingly offensive fœtor. In patients without teeth the gums appear normal.

The first sign of cutaneous bleeding is often to be found on the lower thighs, just above the knees. These hæmorrhages are *perifollicular*—tiny points of bleeding around the orifice of a hair follicle. For some time beforehand the follicle can be seen to be raised above the general surface of the skin, giving the appearance of folliculosis, which is quite commonly seen in varying degrees in people apparently well supplied with ascorbic acid. The condition in scurvy can often be distinguished by its appearance from the follicular keratosis sometimes associated with vitamin A deficiency. In the latter condition there is usually a horny plug of keratin projecting from the orifice of the hair follicle. In scurvy there is a heaping-up of keratin-like material on the surface around the mouth of the follicle, through which a deformed 'corkscrew' hair characteristically projects. Such perifollicular hæmorrhages may subsequently appear on the buttocks, abdomen, legs and arms; they are often followed by petechial hæmorrhages, developing independently of the hair follicles, due to rupture of capillary vessels. Such purpuric spots are usually first seen on the feet and ankles. Thereafter large spontaneous bruises (ecchymoses) may arise almost anywhere in the body, but usually first in the lower extremities, producing the characteristic 'woody leg' (Plate XVIII, A).

Before the changes in the gums and skin appear, the patient has usually felt feeble and listless for some weeks or months. If hard work is expected of him, he may have been suspected of malingering, through absence of clinical signs suggesting disease. Unlike pellagra, in scurvy there is usually no loss of weight through subnutrition.

By the time the disease is fully developed the patient is often anæmic. In a large series of cases, about one-third had severe anæmia, a third moderate anæmia, and the remaining third no anæmia at all (Chapter 14).

Examination of a patient with scurvy usually reveals no abnormal physical signs of disease except gingivitis and cutaneous hæmorrhages and hence the gravity of his condition may not be appreciated. Yet in fact he may die suddenly and without warning, apparently from cardiac failure. Lind himself described how a sailor afflicted with scurvy fell dead while working at a windlass.

Scurvy in infants

Infantile scurvy unfortunately still remains an important disease which may be frequently overlooked. In recent years there have been reports of 79 cases in Toronto (Whelen *et al.*, 1958), 28 in Nagpur (Chakravarty *et al.*, 1958) and 25 in Amritsar (Manchanda & Gupta, 1959). These figures indicate that there is no cause for complacency amongst Child Health workers, responsible for the education necessary to prevent this disease.

Until the teeth have erupted, scorbutic infants do not develop gingivitis. When this occurs the gums have the classical appearance of ‘ scurvy buds ’ described above, a feature of considerable diagnostic importance. The first sign of bleeding is usually a large subperiosteal hæmorrhage immediately overlying one of the long bones—frequently the femur—producing the characteristic ‘ frog-legs ’ position. This gives rise to intense pain, especially on movement. The infant may cry continuously and agonisingly, and scream even louder when lifted.

Diagnosis

The distinctive appearance of the gums must be distinguished from other causes of gingivitis, the commonest of which is periodontal disease (Chapter 54). In the latter condition there are usually accumulations of tartar on the teeth, with retraction of the gum margin. The inflamed rim of the gums is bright red in colour, in contrast to the cyanotic appearance in scurvy, and there is usually much less swelling. In Vincent’s angina the gums are acutely inflamed, ulcerated and painful, but here again the bright red appearance of the lesions is distinctive. Poisoning with heavy metals, particularly lead and mercury, produces a gingivitis in which the gum margin is stained blue ; but there is usually little swelling and the appearance is easily distinguished from scurvy. Dilantin, a drug still sometimes used in epilepsy, may cause marked swelling and hypertrophy of the gums, but they preserve their normal colour and do not bleed.

The perifollicular hæmorrhages of scurvy are distinctive in appearance. But if only petechiæ are visible, other causes of purpura must be excluded, *e.g.* blood dyscrasias, drug poisoning or prothrombin deficiency (Chapter 13). If ecchymoses are the chief manifestation, the patient may be seen first by a surgeon, on the suspicion of some undisclosed traumatic accident.

Scurvy in infants and children may sometimes be mistaken for rheumatic fever or osteomyelitis, because of the pain caused by a subperiosteal hæmorrhage in immediate relation to one of the long bones. The refusal of the child to use one leg may cause the disease to be mistaken for poliomyelitis.

The dietary and social history is invaluable in establishing the diagnosis in doubtful cases. Old solitary people may insist that they fend very well for themselves, but careful questioning will reveal that they do not bother to purchase fresh fruit or vegetables. In other instances the proper foods may be purchased but they are so badly cooked that in fact the diet is made scorbutic.

Special investigations.—Capillary fragility may be increased. This can be shown by the application of a sphygmomanometer cuff to the arm and leaving it inflated for five minutes, half-way between the systolic and diastolic blood-pressure. A shower of petechiæ will then appear over the area of skin below the cuff (Hess test). But this is not a specific test for scurvy ; it may be positive in any of the many states in which capillary fragility is greater than normal.

Ascorbic acid can be estimated with relative ease either in blood plasma or whole blood. This is useful only in excluding the diagnosis, since if any measurable amount of ascorbic acid can be detected in the blood, the case is not one of scurvy. The absence of detectable ascorbic acid, however, does not necessarily indicate that the patient has scurvy, since the blood level of the vitamin falls to unmeasurable levels long before the disease develops (Chapter 14).

A better index of the body reserves of the vitamin is its concentration in the white blood corpuscles. If none can be measured, the diagnosis of scurvy is practically certain.

The estimation of ascorbic acid in the urine provides no reliable aid to diagnosis, because small amounts of the vitamin, or some other substance reducing 2, 6 dichlorophenol-indophenol, continues to be excreted in the urine, even in manifest scurvy. Various ' loading ' tests have been devised whereby one or more doses of ascorbic acid are given by mouth and the amount excreted in the urine subsequently measured. But results of such tests are subject to so many variable factors—the rate of intestinal absorption, the rate at which the tissues are capable of taking up the vitamin or of catabolising it, and the rate at which the kidneys can excrete the temporary excess in the blood—that in our opinion they are of little value in the clinical diagnosis of ascorbic acid deficiency.

Treatment

Because of the danger of sudden death, synthetic ascorbic acid should be given at once and in adequate amounts.) Although preparations are available for intravenous use, parenteral treatment has no advantage over oral administration. (The vitamin is very soluble, readily diffusible and rapidly absorbed—probably from the stomach—even when digestion is seriously impaired. When given intravenously, a large part of the dose is immediately lost in the urine, before the deficient tissues have time to take it up. The aim should be to saturate the body with ascorbic acid with as little delay as possible. The fully saturated body contains about 5 g. of the vitamin, so that a dose of 250 mg. by mouth four times daily should achieve this within a week, despite some loss in the urine which quickly follows each dose.)

It sometimes happens that scurvy arises among people far removed from supplies of synthetic ascorbic acid (*e.g.* among prisoners of war) ; in such situations valuable therapeutic effects are obtained by the use of natural sources of the vitamin such as fresh fruit and vegetables, sprouting peas or extract of pine needles.

Once the danger of sudden death is averted by giving ascorbic acid, attention should be paid to correcting the general deficiencies of the patient's former diet. A liberal diet, including fresh fruit and as much properly cooked vegetables as are available and the patient will accept, should be given. If the patient is anæmic, ferrous sulphate tablets by mouth are indicated.

Finally the doctor must do what he can to correct the social, agricultural and economic circumstances that originally deprived his patient of foods providing ascorbic acid.

Prognosis

With adequate treatment no patient dies of scurvy ; but if treatment is delayed he may die. If the measures recommended above are applied, recovery is usually rapid and complete.

Prevention

It has already been said that in Great Britain at least, scurvy tends to occur at the two extremes of age : infancy and old age. The prevention of scurvy in infants has been accomplished by the better education of mothers and helped by the distribution of cheap, concentrated orange juice of standard ascorbic acid content, through the Welfare Food Service. So far, however, the Welfare State has failed to find any simple administrative means of preventing scurvy among the old and solitary, who are largely unresponsive to education.

Special provision against scurvy is desirable for any group of people living on packed, preserved rations for any length of time such as the explorers of inaccessible lands and oceans, or armed forces defending a barren territory. In such circumstances the bulk of the rations is a prime consideration, especially if airlifts are involved. Tinned fruit and vegetables provide few essential calories in proportion to their weight. Synthetic ascorbic acid tablets are therefore invaluable under such conditions, although some natural but concentrated source of ascorbic acid, *e.g.* orange juice, rose-hip syrup or blackcurrant purée is to be preferred if possible, since it would be better appreciated by the men and therefore more likely to be taken regularly. In default of such supplies antiscorbutic remedies can often be prepared from green herbs on the spot. Scurvy grass (*Cochlearia officinalis*) which grows on seashores is a good source of the vitamin (Meiklejohn *et al.*, 1953) and deserves its traditional reputation among sailors. Infusion of pine or spruce needles is another ancient remedy. Curiously it is not the young, green needles that contain most ascorbic acid but those that are old and darkened.

In times of drought and famine, when fresh vegetables are not available, ascorbic acid can be obtained by the germination of pulses or cereals. A well-tried recipe that has prevented many cases of scurvy in India is: "A sufficient quantity of whole (unsplit) dhal or gram (say 1½ to 2 oz. per man) is soaked in water for 12 to 24 hours. A container big enough to allow for expansion and holding sufficient water should be used. Then pour off the water, remove the grains and spread on a damp blanket in a layer thin enough to allow access of air, and cover with another damp blanket. Keep the blankets damp by sprinkling with water. In a few hours small shoots will appear, and when these are ½ to 1 inch long the process is complete. Vitamin C content is maximal after about 30 hours of germination." Pulses normally contain little or no ascorbic acid. One ounce (30 g.) of dried pulse may on germination yield 9 to 15 mg. of the vitamin, an amount sufficient to prevent scurvy.

The distribution of synthetic ascorbic acid tablets on a large scale to civilian populations is seldom warranted. Ascorbic acid is rarely the sole nutrient lacking in a defective diet; so to give this vitamin alone is an inadequate preventive measure and distracts attention from the essential need of improving the diet.

APPENDIX

An Account of Scurvy afflicting the Men of Jacques Cartier's Expedition to Newfoundland in 1935

Reproduced from Hakluyt's *Principal Navigators* (1600)

"Our Captaine considering our estate (and how that sicknesse was encreased and hot amongst us) one day went foorth of the Forte, and walking upon the yce, hee saw a troupe of those countreymen comming from Stadacona, among which was Domagaia, who not passing ten or twelve days afore, had been very sick with that disease, and had his knees swolne as bigge as a childe of two years old, all his sinews shrunke together, his teeth spoyled, his gummes rotten, and stinking. Our Captaine seeing him whole and sound, was thereat marvellous glad, hoping to understand and know of him how he had healed himselfe, to the end he might ease and help his men. So soone as they were come neere him, he asked Domagaia how he had done to heale himselfe: he answered, that he had taken the juice and sappe of the leaves of a certain Tree, and therewith had healed himselfe: For it is a singular remedy against that disease. Then our Captaine asked him if any were to be had thereabout, desiring him to shew him, for to heale a servant of his, who whilst in Canada and Connacona, was stricken with that disease: That he did because he would not shew the number of his sicke men. Domagaia straight sent two women to fetch some of it, which brought ten or twelve branches of it, and therewithall shewed the way how to use it, and that is thus, to take the barke and leaves of the sayd tree, and boile them togither, then to drinke of the sayd decoction every other day, and put the dregs of it upon his legs that is sicke: moreover, they told us, that the vertue of that tree was, to heale any other disease: the tree is in their language called Ameda or Hanneda, this is thought to be the Sassafras tree. Our Captaine presently caused some of that drink to be made for his men to drink of it, but there was none durst tast of it, except one or two, who ventured the drinking of it, only to tast and prove it: the other seeing that did the like, and presently recovered their health, and were delivered of that sickness, and what other disease soevere, in such sorte, that there were some had bene diseased and troubled with the French Pockes foure or five yeres, and with this drink were cleane healed. After this medicine was found and proved to be true, there was such a strife about it, who should be first to take it, that they were ready to kill one another, so that a tree as big as any Oake in France was spoiled and lopped bare, and occupied all in five or sixe daies, and it wrought so wel, that if all the phisicians of Mountpelier and Lovaine had bene there with all the drugs of Alexandria, they would not have done so much in one yere, as that tree did in sixe days, for it did so prevaile, that as many as used of it, by the grace of God recovered their health."

CHAPTER 32

ORIENTAL BERIBERI

BERIBERI is a nutritional disorder at times widespread in the Orient, caused by eating diets in which most of the calories are derived from highly milled rice.

Three forms are described: (1) wet beriberi in which œdema and cardiac failure occur, (2) dry beriberi, a nutritional polyneuropathy, and (3) infantile beriberi. Thiamine promptly relieves the œdema and circulatory distress, but has no clear-cut effect on the neuropathy (p. 436). Wet and dry beriberi differ greatly in their clinical features, yet they are closely associated epidemiologically. Though caused by the same types of diets, the biochemical lesions responsible may differ in degree or in kind.

History and ætiology

A Japanese naval surgeon, Takaki (1885, 1906), was the first to demonstrate that beriberi is essentially a nutritional disease arising when the proportion of polished rice in the diet is excessive. After studying the disease for a number of years he persuaded the Japanese authorities in 1883 and 1884 to replace a part of the rice in the ration by wheaten bread and to increase the allowance of vegetables and milk. There was a striking reduction in the incidence and mortality of the disease as shown in Table 32, 1.

TABLE 32, 1. *Beriberi in the Japanese Navy*

Year	Force	Cases of beriberi	Deaths from beriberi
1878 . .	4528	1485	32
1879 . .	5081	1978	57
1880 . .	4956	1725	27
1881 . .	4641	1163	30
1882 . .	4769	1929	51
1883 . .	5346	1236	40
1884 . .	5638	718	8
1885 . .	6918	41	0
1886 . .	8475	3	0
1887 . .	9106	0	0

Takaki himself attributed this improvement to an increase in protein intake.

Further observations in the Far East also showed that beriberi was associated with the consumption of rice that had been highly polished in the raw state and that it could be prevented either by adding other foods, as Takaki had done, or by substituting parboiled rice for raw-milled rice. The observations made by Fletcher (1907) in the asylum at Kuala Lumpur (Malaya) shown in Table 32, 2 illustrate this.

Beriberi was also endemic in the Philippine Scouts: in 1909 there were 618 cases. Then 20 oz. of polished rice in their rations was changed to 16 oz. of unpolished rice and 1·6 oz. of dried beans (Vedder, 1913). In 1911 there were only three cases of beriberi and in 1913 none. Numerous other reports of the spectacular eradication of beriberi from amongst people living on diets composed chiefly of highly milled rice appeared between 1900 and 1914. Coincidently the search for the anti-beriberi vitamin, leading later to the isolation of thiamine, was being pursued by laboratory workers. However, those diets associated with beriberi were all seriously unbalanced and deficient in other vitamins besides thiamine.

TABLE 32, 2. *Observations on patients in Kuala Lumpur Asylum* (1907)

Diet	Number of Patients	Cases of beriberi	Deaths
East Ward: Mainly raw polished rice .	124	34	18
West Ward: Mainly parboiled rice . .	123	2	0

Geographical distribution

Beriberi is common throughout the East. It occurs in China, Japan, the Philippines, Thailand, Malaya, Singapore, Indonesia and Burma, *i.e.* wherever raw-milled rice is the staple article of the diet. In India, although beriberi may occasionally be found in any part of the country, it is an important endemic disease only in the coastal region of the Andra province known as the Northern Circars, which runs north from Madras City to Vishakhapatnam. The reason for this is that only in this area is raw-milled rice the principal cereal. In all other parts of India, Pakistan and Ceylon rice is usually parboiled before milling and this conserves the vitamin B complex (Chapter 17) and so prevents beriberi. Indian expatriates in Malaya, Singapore and elsewhere, who continue to parboil their rice, remain remarkably free from beriberi.

Although beriberi is usually associated with a rice diet, this is not invariably the case. The disease may occur in groups consuming excessive amounts of highly milled wheat. A striking example of this was found in the fishermen of Newfoundland and Labrador (Aykroyd, 1930). These men and their families were often cut off through the long winter from all sources of fresh provisions. When their winter stores consisted mainly of large quantities of refined wheat flour, beriberi used to be common. Another example of the disease afflicting wheat-eaters occurred in 1916 when the 3rd Indian Division was besieged by the Turks at Kut-el-Amara (Hehir, 1922). During the siege the Indian sepoys ate whole-wheat chapattis and did not develop beriberi. The British troops ate white bread made from refined wheat flour and beriberi broke out amongst them.

Chemical pathology

In wet beriberi a fundamental biochemical lesion arises as a result of the dietary deficiency of thiamine. Owing to a lack of this vitamin carbohydrates are incompletely metabolised and there is an accumulation of lactic acid and pyruvic acid in the tissues and body fluids. Platt and Lu (1936) found levels of blood pyruvate from 2·4 to 7·5 mg./100 ml. of blood in patients with beriberi and marked œdema. The upper limit of blood pyruvate in healthy persons is about 1·3 mg./100 ml. The local accumulation of these metabolites causes dilatation of peripheral blood vessels, as in normal subjects. In beriberi this vasodilatation may be extreme, so that fluid leaks out through the capillaries, producing œdema. At the same time the blood flows rapidly through the dilated peripheral circulation. The speed with which the blood circulates adds a burden on the heart which is already embarrassed through lack of thiamine needed for the normal metabolism of carbohydrate in the heart muscle. As the disease progresses the weakened myocardium dilates. Eventually congestive heart failure results, which further accentuates the œdema. A feature of this failure is that the speed of the circulation continues to be faster than normal, an example of ‘ high output ’ failure. Sudden death may result from acute myocardial exhaustion.

In dry beriberi these biochemical changes have seldom been reported and the level of blood pyruvate is usually within normal limits.

Morbid anatomy

In wet beriberi the heart at autopsy is found greatly dilated ; there is general œdema of the tissues and serous effusions into the body cavities, often most marked in the pericardium. Microscopic examination usually shows loss of striation of myocardial fibres, which are also finely vacuolated and often fragmented.

In dry beriberi there is severe wasting of soft tissues. In long-standing cases there is Wallerian degeneration of peripheral nerves, both sensory and motor, with extensive demyelination and destruction of the axons. The vagus and other autonomic nerves may be affected. Degenerative changes both in the tracts and in grey matter of the cord are found, but these are usually not so marked as in the peripheral nerves. There may be chromatolysis of cells in the posterior root ganglia, anterior horns and cranial nerve nuclei.

Clinical features

The early symptoms and signs are common to wet and dry beriberi. The onset is usually insidious, though sometimes precipitated by unwonted exertion or a minor febrile illness. At first there is ill-defined malaise, associated with heaviness and weakness of the legs. This may cause some difficulty in walking. There may be a little œdema of the legs or face and the patient may complain of precordial pain and palpitations. The pulse is usually full and moderately increased in rate. There may be complaints of ' pins and needles ' and numbness in the legs. The tendon jerks are usually sluggish, but occasionally slightly exaggerated. Anæsthesia of the skin, especially over the tibiæ, is common. Such a condition may persist for months or even years with only minor alterations in the symptoms. In areas where beriberi is endemic it is often extremely common. The patients are only mildly incapacitated and may continue to earn their living even as manual labourers, but at a very low level of efficiency. At any time this chronic malady may develop into either of the severe forms.

Wet beriberi

The patient often appears well fed. Œdema is the most notable feature which may develop very rapidly and involve not only the legs but also the face, trunk and serous cavities. Palpitations and breathlessness are marked. There may be pain in the legs after walking, similar to the pain that results from ischæmia in muscle (Platt & Gin, 1934). The calf muscles are frequently tense, slightly swollen and tender on pressure. The veins of the neck become distended and show visible pulsations. The apex beat of the heart is displaced outwards. In the arteries there is often a lowered diastolic pressure and a proportionally higher systolic pressure. In consequence on auscultation over the femoral and other large arteries, a curious ' pistol shot ' sound may be heard. The pulse is generally fast and bounding as in aortic regurgitation. Walters (1953) described an outbreak of beriberi amongst pearl divers in Kuwait in which the most striking clinical feature was high blood pressure. Systolic pressures of 200 mm. Hg were recorded. Diastolic pressures were also raised. Myocardial damage persisted long after recovery from the acute attack. If the circulation is well maintained, the skin is warm to the touch owing to the associated vasodilation : when the heart begins to fail it becomes cold and cyanotic, particularly on the face. Electrocardiograms show no consistent changes but in some cases there are low voltages of the QRS complex, inverted T waves or evidence of disturbed conduction. The volume of the urine is diminished, but there is no albuminuria. The mind is usually clear. The patient is constantly in danger of a sudden increase in the œdema, with acute circulatory failure, extreme dyspnœa and death.

Dry beriberi

The essential feature is a polyneuropathy, as further described in Chapter 33. The muscles become progressively more wasted and weak, and walking becomes increasingly difficult. The thin, even emaciated patient needs at first one stick, then two, and may finally become bedridden. The disease is essentially a chronic malady, which may be arrested at any stage by improving the diet. Bedridden patients and those with severe cachexia are very susceptible to infections. When bacillary dysentery or tuberculosis accompany dry beriberi, a fatal result may rapidly occur unless prompt and efficient treatment is given. Patients with dry beriberi are always liable to a sudden onset of œdema which may be due to a variety of dietary causes, *e.g.* lack of protein, calories or thiamine.

The older accounts of beriberi record that cerebral manifestations are uncommon. However, amongst the British prisoners of war in Japanese camps, where beriberi was endemic, there were cases of a cerebral disorder, which usually responded quickly to thiamine therapy. This disorder has been called ' cerebral beriberi ' ; however, we have described the condition under its alternative title of Wernicke's encephalopathy (p. 446) : either designation would appear to be correct.

Infantile beriberi

This is a special form of cardiovascular beriberi, common in endemic areas. It occurs in breast-fed infants, usually between the third and sixth months. The clinical features differ somewhat from the adult disease. It exists in an acute and chronic form. In the former cardiac failure may develop abruptly ; the infant suddenly becomes cyanosed with dyspnœa and tachycardia and dies within a few hours. One characteristic sign—usually encountered only in severe cases—is partial or complete aphonia ; the infant's cry becomes thin ; he may even go through the motions of crying without producing an audible sound. In the chronic form, a state of marasmus develops due to a general failure of nutrition often associated with vomiting and diarrhœa. Œdema may occur but is less common than in the adult form.

Infantile beriberi remains an important problem especially in isolated rural areas in South-East Asia. The diagnosis of the disease in public health practice and the difficulties in prevention have been discussed in a valuable paper by Aykroyd (1957). Postmus (1958) has described the problem in Burma.

Differential diagnosis

A large number of diseases may closely resemble the various forms of beriberi. In endemic areas the diagnosis is usually not difficult. Outside these areas it is unwise to make the diagnosis unless there is a history of a poor diet based on polished rice or other refined cereal.

In mild and chronic cases there may be few or no physical signs and the diagnosis may have to depend on the interpretation of symptoms and the dietary history, often inaccurately described. In prisons and labour forces, such patients may be accused of malingering. The symptoms also closely resemble the manifestations of anxiety states common amongst Europeans.

The œdema of wet beriberi must be distinguished from that associated with hepatic and renal disease and congestive cardiac failure. The hot extremities in cardiac beriberi and the absence of protein in the urine are useful diagnostic points. Famine œdema should seldom be a diagnostic difficulty if a proper dietary history is taken. Wet beriberi and famine œdema seldom occur together in adults. In the past there has been much confusion with epidemic dropsy (Chapter 25).

Cardiovascular beriberi must be distinguished from other causes of high output cardiac failure, notably hyperthyroidism and severe anæmia, both of which may produce many of the same clinical features. In all doubtful cases of wet beriberi the therapeutic response to thiamine will settle the diagnosis.

Cardiovascular beriberi is by no means the only nutritional cause of heart failure. The sudden failure that may occur in scurvy is referred to in Chapter 31. Some of the cases described as resembling beriberi by Weiss (1940) and Dock (1940) occurring among alcohol addicts in the U.S.A. did not respond to thiamine. Several medical officers who treated prisoners held by the Japanese have described other types of heart failure, sometimes accompanied by acute hypertension, occurring in association with severe malnutrition but differing clinically from typical beriberi. Gillanders (1951) described for the first time a form of nutritional heart disease occurring in African Bantus. It is characterised by a very large heart, massive œdema and associated hepatic damage. The disease did not respond to thiamine, but only to a good general diet.

There seems to be little doubt that several types of nutritional failure, besides thiamine deficiency, can so weaken the myocardium that cardiac failure results. The subject has been well reviewed by Pallister (1952).

The features of dry beriberi are sometimes indistinguishable on clinical examination from other forms of nutritional, infective and toxic polyneuropathy (Chapter 33). The differential diagnosis is accordingly based on the presence or absence of a history of nutritional deficiency and of such ætiological factors as alcoholism, the ingestion of toxic substances or an infective illness. In endemic areas the disease may be confused with neuritic leprosy. Neuritic leprosy is characterised by palpable, cord-like superficial nerves and areas of skin anæsthesia. These two diseases not infrequently occur together and when they do, dry beriberi, if mild, may be overlooked. Cutaneous ulcers are occasionally infected with *C. diphtheriæ* and, if the ulcers are on the shins, the clinical picture of diphtheritic neuritis in the lower limbs is very similar to dry beriberi. The increasing use of chemical pesticides and weed-killers in Eastern agriculture—if not properly supervised—may well give rise to toxic neuropathies resembling dry beriberi.

The diagnosis of infantile beriberi may be difficult. Neither œdema nor paralysis is an early sign and sudden death may occur before either is present. In cases of doubt the presence of minimal signs or symptoms of beriberi in the mother may decide the issue. A history of the sudden death of a previous child between the ages of 3 and 9 months is highly suggestive. In public health practice among a rice-eating community, a rise in death-rate of infants should suggest the possibility that infantile beriberi has become endemic.

Treatment

Wet beriberi must be treated as soon as the diagnosis is made, because fatal heart failure may occur with great suddenness. Complete rest is essential and thiamine should be given at once to correct the causative biochemical lesion: 10 mg. of synthetic thiamine hydrochloride, two or three times a day, may be life-saving. In severe cases the first two or three doses should be given intramuscularly or intravenously. When the emergency is overcome—or initially in milder cases—the oral route is satisfactory and should be preferred. There is usually no advantage in giving larger doses.

The prompt response of a patient with cardiovascular beriberi to thiamine is one of the most dramatic events of medicine. Within a few hours the breathing is easier, the pulse-rate slower, the extremities cooler and a rapid diuresis begins to dispose of the œdema. Within a few days the size of the heart is restored to normal.

With relief of the cardiac emergency, the patient may still be incapacitated as a result of other deficiencies in his former diet. A good mixed diet with less emphasis on rice is needed. Whole wheat, millet or some other cereal should, if possible, be substituted for part of the rice in the diet. Pulses have a well-deserved reputation for curing and preventing beriberi; 120 g. (4 oz.) of beans or lentils are a useful daily addition to the diet. Any foods of animal origin that are available should be included. The diet can be supplemented usefully by natural sources of the entire vitamin B complex such as yeast, liver extract, wheat germ, rice polishings or yeast extract. Half an ounce or more of dried yeast is a valuable remedy for aiding recovery. Rice bran, if fresh and of good quality, is also useful and sometimes more readily obtainable. Half an ounce can usually be taken daily without digestive disturbance. This should provide about 0·3 mg. of thiamine, but samples vary widely in their content. Rice bran rapidly goes rancid, but if it can be defatted it will keep indefinitely and does not lose its content of the B vitamins.

In dry beriberi there is no dramatic response to thiamine and no proof that progress is hastened by parenteral treatment with any vitamin preparation. A dietary regime similar to that recommended for convalescent cases of wet beriberi is recommended. This should be supplemented by one of the concentrated sources of the B group of vitamins mentioned above, together with oral thiamine. In both forms of the disease, preoccupation with dietary treatment should not divert attention from treating the patient with good nursing, management of associated infections, physiotherapy and subsequent rehabilitation.

The simplest way to treat infantile beriberi is via the mother's milk.

The mother should receive 10 mg. thiamine hydrochloride twice daily—in severe cases by injection. Thereafter the mother should receive a good diet, supplemented if possible by yeast or rice bran. If these are not available, 1 mg. of thiamine hydrochloride, three times a day, should be given by mouth to the mother.

Prevention

In principle this is easy. All that is necessary in endemic areas is to prevent the production of over-milled rice or wheat. In practice, however, there are many difficulties in the control of milling processes. These are discussed on page 276 as also is the fortification of cereals with vitamins.

In prisoner-of-war camps in the Far East, various naturally occurring yeast preparations were made. These were useful in some instances but their prophylactic value was variable and never as good as brewers' yeast.

Wherever possible, it is desirable to reduce the proportion of rice in the diet and encourage the growth of alternative crops and protective foods. This may involve changes in agricultural policy. Much can sometimes be done with small gardens, properly cultivated. The substitution of parboiled rice for raw-milled rice will also greatly reduce the incidence of beriberi. In practice it has been found very difficult to persuade people to change their customs and give up eating raw-milled rice. Ignorance of the relative nutritional values of different foods is usually a contributory factor and this can only be overcome by better education.

CHAPTER 33

NUTRITIONAL NEUROPATHIES

BEFORE discussing the neurological disorders that arise in man as a result of dietary deficiencies, it is useful to consider some basic scientific principles about the nutrition of the nervous system. Since the first experiments of Eijkman (p. 222) at the end of the last century, it has been realised that the nervous system is susceptible to damage from dietary causes. This is scarcely surprising since the nutritional welfare of this system is dependent on a finely adjusted mechanism requiring a source of energy derived only from carbohydrate of which it has no immediate store, and a variety of highly complicated enzyme systems which govern and control the use of this energy. All the raw materials for the specialised functions of the nervous system must come from the diet, and obviously they are many. It not only needs carbohydrate as fuel, but also the enzymes to handle it.

So far as modern knowledge goes, the enzymes that the nervous system requires include cocarboxylase, transaminase and coenzyme A. The prosthetic groups of these enzymes contain thiamine, pyridoxine and pantothenic acid respectively. Cyanocobalamin is also needed.

In this chapter a description is given of various neuropathies which arise only when there is either a definite history of a gross defect in the quality or quantity of the food or clear evidence of a digestive disturbance leading to failure of absorption. There is thus good evidence that they are primarily nutritional in origin. They are mostly chronic conditions and as such present a strong contrast to the clinical features of certain other nutritional disorders, such as the heart failure of wet beriberi and the hæmorrhagic manifestations of scurvy, which usually respond dramatically to treatment with the appropriate vitamin. In such disorders the therapeutic response enables the diagnosis to be made and the ætiology to be stated with confidence. Nerve cells, however, have limited powers of recovery compared with other cells ; hence disorders of the central or peripheral nervous system, unless mild in degree or recent in origin, are associated with structural changes that are largely irreversible. No sudden or striking diminution of symptoms or signs in any chronic disease of the nervous system with structural changes can be expected to follow dietary or vitamin therapy.

Classification

Clinical knowledge of the dietary neuropathies was greatly advanced by the bitter personal experience of prisoners in Japanese hands during the Second World War. Full details will be found in several excellent accounts that have since been written by Spillane (1947), Denny-Brown (1947), Smith and Woodruff (1951) and Cruickshank (1952). A convenient classification, adopted in the following pages, is based on that proposed by Cruickshank.

Group I—where the lesion is predominantly in the peripheral nerves. This group includes :—

- (*a*) The polyneuropathies of beriberi, alcoholism and pregnancy.
- (*b*) The ' burning feet ' syndrome.

Group II—where the lesion is predominantly in the central nervous system. This group includes :—

- (*a*) Wernicke's encephalopathy.
- (*b*) Nutritional amblyopia.
- (*c*) The cord syndromes—spinal ataxia ; spastic paraplegia and lathyrism ; subacute combined degeneration of the cord.

NUTRITIONAL POLYNEUROPATHY

This is a disease characterised by signs of bilateral and usually symmetrical lesions involving the peripheral nerves, both sensory and motor, with a dietary history indicating a failure in nutrition as the primary cause. The polyneuropathy of dry Oriental beriberi is the classic example. In countries outside the tropics an essentially similar disease occurs not infrequently in chronic alcoholics and rarely during pregnancy and in the malabsorption syndrome.

These disorders have been described in the past as ' multiple nutritional polyneuritis,' but since there is no evidence of an infective or toxic inflammation, the term ' polyneuropathy ' is preferable.

History

Edwin Bramwell (1925) questioned whether " it was not possible that a food factor—a deficiency of vitamins—might be of ætiological moment " in some obscure cases of multiple neuritis. Three years later, Shattuck in the U.S.A. independently made the same suggestion. In 1933 Minot *et al.* (1933) published their observations showing the nutritional origin of polyneuropathy arising in alcoholism and pregnancy ; they pointed out its similarity to dry beriberi.

The chemical isolation of thiamine in 1936 led to its widespread use in a great variety of neurological conditions, in the optimistic belief that it was the hypothetical ' antineuritic vitamin.' The first reports were enthusiastic, but when critically reviewed (Meiklejohn, 1940) it was apparent that no reliable evidence had been presented to show that thiamine caused any striking improvement in the clinical features of diseases associated with structural changes in the nervous system. This was scarcely surprising in view of the irreversible nature of such neurological lesions. However, there was evidence that thiamine sometimes relieved muscular pain and weakness ; but these symptoms are more likely due to the acute biochemical lesion of thiamine deficiency in the muscles, as occurs in cardiovascular beriberi, than to organic lesions in the peripheral nerves.

Ætiology

Nutritional polyneuropathy is a common but inconstant feature of Oriental beriberi, which arises from the consumption of poor diets composed chiefly of rice. In the Western world nutritional polyneuropathy is seen most often in chronic addicts to alcohol. It was thought at one time that alcohol was itself a specific neurotoxin and directly responsible for the lesions in the peripheral nerves ; yet acute overdosage with alcohol produces no neuropathy. The work of Minot and others has amply shown that the true cause is nutritional failure. Alcohol provides calories, but none of the other essential nutrients needed for the normal metabolism of the nervous system.

In view of what has already been said, it is obviously rash to ascribe the cause of nutritional polyneuropathy to lack of any one single dietary nutrient. The original search for the hypothetical ' antineuritic vitamin ' opened up a vast field of research into the nutritional needs of the nervous system with consequent advances in knowledge ; but it is clear now that no single vitamin—thiamine, pyridoxine or pantothenic acid—is the specific ' antineuritic vitamin.' As Spillane (1947) rightly said : " If general experience in the last 10 years had established the specificity (of thiamine) in the treatment (of nutritional polyneuropathy) we should not now have to debate the question." Perhaps Admiral Takaki was nearer to the truth than has recently been supposed when he attributed neuritic beriberi to lack of protein. Neuropathies of almost every kind occur most frequently in thin, underfed people. The wasting of the muscles is often too extensive to be blamed solely on degeneration of the nerves supplying them ; it suggests that the body has been drawing on its tissue proteins as a source of energy over a long period, perhaps creating a shortage of the enzymes on which the integrity of the nervous system depends.

Morbid anatomy

At autopsy, morbid anatomical changes are found in both sensory and motor peripheral nerves. The earliest change is simple demyelination of the fibres at the point farthest away from the cell bodies of the fibres. Later the nerve fibres themselves become fragmented and disintegrate (Wallerian degeneration.)

Clinical features

The patient is usually unduly thin, in contrast to the common appearance of patients suffering from cardiovascular beriberi. The earliest symptoms are weakness and paræsthesia in the legs. Hyperæsthesia, nocturnal cramps, ataxia (due to loss of proprioceptive sensation) and foot-drop frequently follow. Both sensory and motor nerves are involved, usually chiefly in the legs but also in severe cases, in the arms and trunk. On examination the sensory changes are shown by loss of position and vibration sense, and by areas of anæsthesia—preceded by hyperæsthesia—in the skin. Degeneration of the motor nerves results in muscular wasting and loss of tendon reflexes. As in all lower motor neuron lesions, the plantar responses remain flexor. Nerve deafness is a common accompaniment. The disease is essentially chronic, developing slowly and leading to gradual incapacity so that the patient needs the aid of sticks to get about, and eventually may become bedridden ; in which event bedsores and contractures make nursing very difficult.

Differential diagnosis

There are many diseases which—by involving the peripheral nerves—may mimic nutritional polyneuropathy. These include the polyneuropathies that are occasionally seen in patients with carcinoma of the bronchus, periarteritis nodosa and acute porphyria. Drugs and poisons of several kinds can produce the same clinical picture, such as isoniazid, arsenic, di-orthocresyl phosphate and other organic phosphates now used as insecticides. Diabetic neuropathy sometimes resembles nutritional polyneuropathy, and may have a common fundamental ætiology in the lack of essential enzymes in the nerves ; usually, however, it differs in being random in its distribution, affecting any nerve—sensory, motor or autonomic—in an asymmetrical manner. Its most common and characteristic presenting symptom is pain in the limbs in bed at night. The one simple diagnostic criterion of nutritional polyneuropathy is whether there is evidence to suggest nutritional failure. Without this evidence from the clinical history the diagnosis should not be made.

In some cases of polyneuropathy apparently unconnected with nutritional failure, an impaired carbohydrate metabolism is present as revealed by an abnormal elevation of blood pyruvate following a test dose of glucose (Thompson, 1952). The most likely explanation is that many chemico-pathological disorders involve the metabolism of carbohydrate and, since the nervous system is entirely dependent on carbohydrate to supply its needs for energy, all such disorders are especially likely to affect the nervous system.

Treatment

This demands first, attention to the patient's diet both in quantity and quality. The neurological lesions will not improve until the patient regains his strength, so every effort should be made to restore him to his original body weight. Plenty of protein—milk, eggs, meat, fish—is desirable, supplemented by natural sources of the vitamin B complex—yeast or yeast extract (*e.g.* Marmite), liver extract, rice bran or wheat germ. This may be difficult to provide for poor, rice-eating sufferers from beriberi and unacceptable to alcoholic patients with gastritis, or pregnant women who have been vomiting after every meal. The physician's art must be adapted to find the best means of supplying these needs for the individual patient.

The value of synthetic thiamine is disputed. There is no satisfactory evidence that its administration has improved in any striking way the objective signs of nutritional polyneuropathy.

Prevention

The disease as it occurs among rice-eaters can be prevented by the same general measures described for the prophylaxis of cardiovascular beriberi. Its occasional occurrence in alcoholics and sufferers from chronic vomiting of whatever cause can only be prevented by attention to the malady that conditioned the nutritional failure.

BURNING FEET SYNDROME

Outbreaks of this distinct clinical syndrome have occurred at various times in Europe, Central America, Africa and India among people living on very poor diets. It became very troublesome among European prisoners in the Far East during the Second World War. Excellent descriptions of the condition have been provided by Smith and Woodruff (1951) and by Cruickshank (1952).

The earliest symptom is aching, burning or throbbing in the feet. This becomes more intense and is followed by sharp, stabbing, shooting pains, which may spread up as far as the knee like an electric shock, causing excruciating agony. They come on in paroxysms and are usually worse at night. Most patients get some relief by walking about, and sufferers may spend the night limping up and down outside their quarters. Some manage to get relief by wrapping their feet in cold wet cloths or sitting with their feet in a pail of cold water. Repeated pain and loss of sleep produce a thin, exhausted, red-eyed, irritable patient.

In contrast to the striking symptoms, objective signs of neuropathy are seldom marked unless the polyneuropathy of beriberi coexists. The tendon jerks are usually normal but may be exaggerated. In the great majority of cases there is no demonstrable sensory change ; indeed there is some doubt whether the syndrome should properly be classified as a neuropathy. It may be due chiefly to peripheral vascular changes (Cruickshank, 1952). On the other hand there seems to be no constant change in skin temperature. Some patients develop a transient hypertension during the course of an attack. Smith and Woodruff (1951) hold the view that the probable sites of the lesion are the posterior root and sympathetic ganglia.

The syndrome results from the prolonged consumption of a diet deficient in protein and the B group of vitamins. Patients who suffer from it may also develop the orogenital syndrome (p. 477) or nutritional amblyopia (p. 447), but rarely frank beriberi. Gopalan (1946) in Madras reported the symptoms were promptly relieved in most patients by injections of calcium pantothenate. However, in a controlled trial in Ceylon (Bibile *et al.*, 1957) pantothenic acid produced no significant improvement. Perhaps the syndrome may be produced by a variety of poor diets. Patients improve when given yeast, Marmite, rice polishings, soya beans and other foods rich in the vitamin B complex.

WERNICKE'S ENCEPHALOPATHY

This disease is caused by an acute biochemical lesion in the brain through lack of essential nutrients to maintain normal metabolism. The principal deficiency concerned is almost certainly lack of thiamine; indeed the disease may be considered the human counterpart of the encephalopathy produced in animals by acute deprivation of this vitamin.

Two of the original three patients described by Wernicke in 1881 were addicted to alcohol. The majority of cases subsequently described in Europe and the U.S.A. have been in alcoholics, although it occasionally occurs as a result of carcinoma of the stomach, pregnancy toxæmia, prolonged vomiting, diarrhœa or other causes of gross digestive failure. De Wardener and Lennox (1947) described 52 cases occurring in European prisoners of war in Singapore, associated with outbreaks of beriberi. Curiously, however, cerebral symptoms are rare in Asiatics with beriberi (Vedder, 1913).

The earliest clinical features are often effortless vomiting, diplopia and nystagmus. These signs should arouse suspicion in any patient who may be deficient in thiamine through alcoholism or a poor rice diet. Mental changes soon follow, and may include apathy, emotional disturbances, loss of memory, disorientation, confabulation and hallucinations. This group of mental symptoms is often called ' Korsakoff's psychosis.' Any of the muscles of the eye—extrinsic or intrinsic—may become involved, sometimes with complete ophthalmoplegia. A peripheral polyneuropathy frequently coexists. The patient soon lapses into stupor and frequently dies unless quickly treated. At autopsy the brain appears normal to the naked eye, but microscopic examination reveals scattered foci of greatly dilated, congested capillaries, sometimes with minute hæmorrhages. They are found most often in the mammillary bodies and in the region of the oculomotor nuclei.

Dramatic therapeutic responses have been obtained in early cases by the parenteral administration of thiamine. De Wardener and Lennox, whose supplies of thiamine were extremely limited, obtained recovery with as little as 2 to 4 mg., after which treatment was continued with yeast preparations. When ample supplies are available it is best to give large doses of thiamine hydrochloride intramuscularly until the major clinical features are relieved (Phillips *et al.*, 1952). Thereafter treatment should be continued with an ample diet (if possible) and some natural supplement of the entire vitamin B complex. When treatment is started early, recovery is usually complete, but if delayed the mental changes may persist.

NUTRITIONAL AMBLYOPIA

A progressive failure of vision attributable to a retrobulbar neuropathy occurred amongst prisoners of war in the Second World War. Denny-Brown (1947) reported a number of cases in British and Indian soldiers admitted to military hospitals in India after release from Japanese camps. In Egypt also, about a hundred cases occurred among German prisoners of war who had suffered for some time previously from chronic dysentery. Similar amblyopias had been described before: in beriberi, pellagra, subacute combined degeneration of the spinal cord and the orogenital syndrome. Fitzgerald Moore (1937) reported many cases in Nigeria between 1930 and 1940. Disturbances of vision, however, are seldom mentioned in accounts of pellagra and beriberi. The incidence of the condition in prisoners of war aroused renewed interest and discussion, though little new was learned about its ætiology.

All the patients appear to have had one feature in common—a period of many months on diets grossly deficient in respect of many essential nutrients. There are thus good reasons for thinking that the disorder is nutritional in origin. The nature of the diets held to be responsible has been very variable. It would appear unlikely that a deficiency of any single nutrient or of any constant association of nutrients is responsible. The possibility that there might be some common toxic agent—such as methyl alcohol, which can cause permanent blindness—responsible for some outbreaks has been extensively but inconclusively explored.

A typical history is that in over a period of 3 weeks or so there is a growing inability to see the colours of small objects. A mist obscures the central field of vision and gradually becomes so intense that it becomes impossible to recognise acquaintances. There is usually no pain, but sometimes the eyes smart. Tinnitus, deafness and dizziness—apparently due to associated involvement of the eighth nerve—sometimes coexist. In the Japanese camps none became completely blind, but several were severely incapacitated.

On examination of the visual fields a central or paracentral scotoma is always present. The visual acuity varies greatly; in some there is little impairment; in others it may be as low as 6/60. In mild cases the retinæ appear normal on examination with an ophthalmoscope. When the loss of vision is severe, temporal pallor is usually present, but in some cases with visual acuity less than 6/60 the retinæ may appear normal.

When the symptoms are not severe they are relieved rapidly by a good diet supplemented by yeast or Marmite, but when vision is markedly affected little or no improvement results from any form of treatment (Clarke & Sircus, 1952; Rodger, 1952).

SYNDROMES INVOLVING THE SPINAL CORD

PELLAGRA

Lesions of the spinal cord sometimes occur in pellagra (p. 453). They appear most often in very chronic cases, late in the disease. The dorsal and lateral columns are often both affected.

SPINAL ATAXIA

Patients who have been living for long periods on diets deficient in the B group of vitamins occasionally develop neurological signs that indicate that the principal lesion is in the posterior columns of the spinal cord, involving particularly proprioceptive sensation. The gait is unsteady and the patient is unable to stand upright without swaying when the eyes are closed (Romberg's test). Vibration sense in the legs is often lost. The condition has been described in association with nutritional amblyopia by Landor and Pallister (1935) in Malaya and by Spillane and Scott (1945) in prisoners of war. We ourselves have seen two cases in strict vegetarians who eat no foods of animal origin. Probably the essential dietary deficiency is lack of vitamin B_{12}, which occurs only in foods of animal origin or in foods fermented by micro-organisms. In other words, the disease may be a form of subacute combined degeneration of the cord, but due to a *direct* dietary deficiency of vitamin B_{12}, in contrast to the *conditioned* deficiency that occurs in Addisonian anæmia. Nutritional spinal ataxia is seldom associated with significant macrocytic anæmia, presumably because a vegetable diet generally supplies sufficient folic acid.

SUBACUTE COMBINED DEGENERATION OF THE CORD (SCD)

This disease is a form of spinal ataxia characterised by degenerative changes in the posterior and lateral columns of the spinal cord occurring in association with Addisonian anæmia. The essential cause is a failure of secretion of intrinsic factor by the stomach leading to a failure of absorption of vitamin B_{12} (p. 237).

SPASTIC PARAPLEGIA

Lathyrism

Lathyrus sativus is a drought-resistant pulse, widely grown in parts of Asia, Africa and Southern Europe, as already described in Chapter 25. If eaten in excessive amounts, it gives rise to lathyrism.

The onset of lathyrism is usually sudden. A patient may go to bed well and wake up paralysed ; or he may fall down at the plough. Sometimes backache and stiffness of the legs precede the onset of the paralysis by a few days. The condition is a spastic paralysis of the lower limbs, due, presumably, to a precisely localised lesion of the lower parts of the pyramidal tracts. The motor nerves to the muscles of the trunk, upper limbs and sphincters are spared. The sensory nervous system is not involved. In mild cases there is only stiffness and weakness of the legs. In more severe cases the patient walks with bent knees on tiptoe. The legs are often crossed ; a ' scissors gait ' develops and walking is only possible with the aid of sticks. In severe cases paraplegia in flexion follows, and walking becomes impossible. The patient can only move about by pushing himself along, supporting his body on his hands, buttocks and heels. The paralysis is typically spastic with greatly increased ankle and knee jerks, and with clonus. The final stage of the disease is completely incapacitating and the sufferers may move to the cities where they are easily recognised amongst the beggars.

Extensive searches for a possible toxic agent have been made. Various extracts of *Lathyrus sativus*, and of various other pulses that are sometimes grown with it, have been examined. Some of these extracts have been proved toxic to experimental animals, but not consistently, at least in quantities comparable to those likely to be consumed by man. The principal accounts are mostly in the Indian and Spanish medical literature, but a useful British review with many references is available (Anon., 1953). That a specific plant poison is not solely responsible is strongly suggested by the fact that a spastic paraplegia—clinically indistinguishable from lathyrism—is not uncommon in parts of the world where lathyrus is not eaten.

Epidemic lathyrism is essentially a disease of famine since the pulse is only eaten in large quantities when the main crops have failed. It would appear then that long periods on an inadequate diet, deficient in calories, proteins and vitamins, predispose to nutritional spastic paraplegia. This does not exclude the possibility that plant toxins may be another precipitating factor. Pathological studies have been very limited, but there is no evidence to suggest a virus or other infective agent.

There is no specific treatment. All patients need a good diet. Minor cases may make a complete recovery following satisfactory dietary and physical rehabilitation. In most cases the pathological changes are irreversible and, as already stated, the patients readily drift into beggary and become an important social problem.

Other forms of spastic paraplegia

Spastic paraplegia in adults is frequently seen in Asia and Africa. Thus out of 2530 consecutive neurological patients admitted to the Royal Hospital, Bagdad, 84 had spastic paraplegia of uncertain origin (Al-Witry *et al.*, 1950). Many Indian hospitals could probably provide the same experience. In the Belgian Congo, Lucasse (1952) found 34 cases in 117 villages ; the local name is ' kitondju.' Spastic paraplegias, very similar to lathyrism, were reported amongst prisoners of war both in the Far East and in Egypt. The great majority of these patients had never at any time in their life eaten lathyrus, but had subsisted for many months on an inadequate diet. Cruickshank (1956) reports 100 patients in Jamaica, of both sexes, between the ages of 10 and 70 who suffered from pyramidal tract damage, but commonly, in addition, urinary disturbances and disorders of proprioceptive sensation. A quarter of his patients showed evidence of retrobulbar neuropathy and a few suffered from nerve deafness. These additional features serve to distinguish it from lathyrism. A further distinction is that the onset is often gradual. Maximum incapacity occurs within a few months and the disease thereafter appears to be stationary. The diet of Cruickshank's patients varied from good to very poor ; they showed no overt signs of vitamin deficiency or malnutrition. He discusses the possibility of a toxic dietary factor as the cause—perhaps derived from ' bush teas ' (p. 531). A further discussion of this and other neurological disorders in Jamaica is given by Cruickshank *et al.* (1961).

CHAPTER 34

PELLAGRA

DEFINITION

PELLAGRA is a nutritional disease endemic among poor peasants who subsist chiefly on maize (Indian corn). It is chronic and relapsing, with a seasonal incidence. The typical clinical features are loss of weight, increasing debility, mental changes, gastrointestinal disturbance—often with persistent diarrhœa—and an erythematous dermatitis brought on by the first sunshine of spring. Pellagra has been called the disease of the three D's : ' dermatitis, diarrhœa and dementia.'

History

It is a relatively new disease—unknown to classical and mediæval physicians, and first described as a clinical entity by Casal in Spain in 1730. He recognised it as a disease of poor people and associated it with the consumption of maize. The introduction of maize into Northern Italy established pellagra there as a severe and still surviving endemic disease. Francesco Frapolli of Milan named it in 1771 (*pelle*= skin : *agra*=sour).

Geographic distribution

Pellagra has occurred all over the world, wherever maize has become the staple cereal. In Europe it spread from Spain and Italy to France, Yugoslavia, Rumania, Bulgaria and then into the Ukraine. Great epidemics have arisen all over North Africa and especially in Egypt. In the last 50 years it has spread to other parts of Africa. Maize eaters in India and Central Asia still suffer from it. It is also well known in Latin America, probably the original home of the disease.

It first became an important disease in the Southern States of the U.S.A. in the early years of this century, as a result of the poverty that followed the Civil War, coupled with increasing dependence on maize. The remarkable fact that pellagra has vanished from the Southern States, whereas before the Second World War it afflicted tens of thousands of poor country folk, demonstrates in a dramatic way that the disease is preventable.

Isolated cases of pellagra occur among people who are not dependent on maize. It is a well-recognised complication of chronic alcoholism in the U.S.A., though curiously rare among similar patients in Europe. A generation ago it was frequently reported among the inmates of lunatic asylums in Great Britain. The poor diet given to mental patients at that period, their frequent unwillingness to eat, coupled with recurrent outbreaks of infectious diarrhœa in the asylums, all contributed to its development. Certainly any chronic disease of the gastrointestinal tract, leading to malabsorption, may result in the development of one or more of the clinical features of the disease.

Ætiology

The history of the search for the cause of pellagra well illustrates how the growth of knowledge can bring together apparently opposing theories and shows—in the end—that each has a substance of truth.

1. **The maize theory.**—Casal himself believed that the disease was connected with eating maize. With the discovery of bacteria in the nineteenth century it became a common idea that any disease in which no causative infective organism could be found, was probably due to ' toxins ' made by bacteria, either inside or outside the body. Pellagra was attributed to some hypothetical toxin in the maize, perhaps produced by bacterial fermentation during storage.

2. **The protein deficiency theory.**—It was soon clear that the diet of impoverished pellagrins was poor in protein and this deficiency was first suggested as the cause of the disease nearly a century ago. This theory gained support when Wilson (1921) in Egypt showed how closely pellagra was linked to an insufficient intake of good quality protein.

Goldberger, whose classic studies of the disease in the Southern States of the U.S.A. led to its ultimate elucidation and eradication, was at first inclined to the view that deficiency of protein, and in particular of the amino acid tryptophan, was the essential cause. Later, however, his concept of the cause of the disease was altered by the discovery that extracts of yeast and liver contained a heat-stable, non-protein factor that would cure both human pellagra and black-tongue in dogs.

3. **The vitamin deficiency theory.**—The investigation of black-tongue in dogs ultimately led to the identification of nicotinic acid as the pellagra-preventing (P-P) factor (p. 229).

Reconciliation of the three theories.—The dramatic therapeutic effects of nicotinic acid in pellagra at first seemed the final proof of the last of these theories, with the result that the two alternatives were temporarily forgotten, until revived by the results of subsequent research.

It still remained to be explained why the disease is so closely associated with the consumption of maize. Maize actually contains more nicotinic acid than oats, rye and white wheaten bread though less than whole wheat. Aykroyd and Swaminathan (1940) pointed out the surprising fact that maize diets in a part of India where pellagra is endemic contain more nicotinic acid than poor rice diets in other regions where it is rare. It has been suggested that maize contains an ' antivitamin,' probably a chemical analogue of nicotinamide that competes with it in metabolic processes but fails to achieve the same effects (Wooley, 1947). The more likely explanations are that some of the nicotinic acid in maize is present in a bound form, unavailable to the consumer (Kodicek, 1940); also the protein of maize, zein, is particularly deficient in the amino acid tryptophan, from which the tissues of the body are able to make nicotinic acid (p. 229).

Goldberger recognised the therapeutic value of milk in pellagra and was inclined to attribute this to its content of tryptophan. Milk, as we now know, contains little nicotinic acid, but is rich in tryptophan.

Thus it has come about that all three of the original theories, though initially apparently contradictory, have proved to be justified. For further details the reader is referred to an excellent review of the subject by Dame Harriet Chick (1951).

OTHER ÆTIOLOGICAL FACTORS IN PELLAGRA.—It is necessary to emphasise that pellagra is a syndrome associated with a variety of clinical features. Although the most outstanding of these—the dermatitis and diarrhœa—respond rapidly to nicotinic acid, there are others that respond less readily, or not at all. The improvement in the mental state of the patient under nicotinic acid therapy is sometimes disappointing, perhaps partly because the associated subnutrition may contribute to its causation (p. 228). The oro-genital and spinal cord changes, the anæmia and hypoproteinæmia, which are all recognised features of the syndrome, are clearly due to deficiencies other than that of nicotinic acid. In the words of McLester and Darby (1952): " While lack of nicotinic acid dominates the picture, pellagra is in truth a disease of multiple deficiencies—nicotinic acid, protein, riboflavin and perhaps hæmopoietic factors."

Gopalan and Srikantia (1960) have produced evidence that a relative excess of leucine may contribute to pellagra. Leucine, if given by mouth, increased urinary excretion of N-methyl nicotinamide in healthy subjects and in patients with pellagra. Leucine also produced a temporary deterioration in the mental condition of two patients. Rice contains much less leucine than maize (p. 83) and this may partially explain why rice-eaters seldom suffer from pellagra.

Chemical pathology

The metabolic disturbances in the body that produce the clinical features of pellagra result in no easily detectable chemical abnormality in the blood or urine, like the accumulation of pyruvic acid in thiamine deficiency. N-methyl nicotinamide, a normal excretory product of nicotinic acid and tryptophan appears in reduced amounts in the urine. However, its measurement in the urine provides no diagnostic test of pellagra. Examination of the blood may reveal anæmia and hypoproteinæmia, due to the associated dietary deficiencies. The anæmia may be macrocytic or microcytic, depending on the predominant associated deficiency.

Morbid anatomy

There are no distinctive changes to be seen at autopsy, though subsequent microscopic sections of the spinal cord may show the degenerative changes in the posterior and lateral tracts that account for the neurological signs observed in life.

Clinical features

General.—The patient is often under-weight, and presents the general features of subnutrition.

Skin.—The diagnosis is generally first suggested by the appearance of the skin. Characteristically, there is an erythema resembling severe sunburn, appearing symmetrically over the parts of the body exposed to sunlight, especially the backs of the hands, the wrists and forearms, face and neck. Exposure to trauma or mechanical irritation of the skin may also determine the site of the lesion. The skin in the affected areas is at first red and slightly swollen ; it itches and burns. In acute cases the skin lesions may progress to vesiculation, cracking, exudation and crusting with ulceration and sometimes secondary infection ; but in chronic cases the dermatitis occurs as a roughening and thickening of the skin with dryness, scaling and a brown pigmentation (Plate XVIII, B).

Digestive system.—Complaints of digestive upset are usual, and diarrhœa is common but not always present. There may be nausea, a burning sensation in the epigastrium, and sometimes constipation in chronic cases. The digestive symptoms may be aggravated by the presence of intestinal parasites. The mouth is sore and often shows angular stomatitis and cheilosis (Chapter 37). The tongue characteristically has a ' raw beef ' appearance—red, swollen and painful, though usually without loss of papillæ. Secondary infection of the mouth with Vincent's organisms is common. It is probable that a non-infective inflammation extends throughout the gastrointestinal tract and accounts for the diarrhœa ; certainly the rectum and anus are frequently inflamed. The diarrhœa is characteristically profuse and watery, sometimes with blood and mucus in the stools, and accompanied by tenesmus.

Nervous system.—In the milder cases the symptoms consist chiefly of weakness, anxiety, depression, irritability and failure of concentration ; in severe cases delirium is the commonest mental disturbance in the acute form of the disease and amentia in the chronic form. Because of these changes, chronic pellagrins may be admitted to mental hospitals. In chronic cases there may be signs of degenerative changes in the posterior and lateral columns of the spinal cord—decreased sensation to touch and loss of vibration and position sense are often accompanied by hyperæsthesia and paræsthesia in the feet. The loss of position sense may give rise to ataxia. Spasticity and exaggerated tendon reflexes give evidence of involvement of the pyramidal tracts. Alternatively there may be foot-drop, and impairment of tendon reflexes, indicating a peripheral nerve lesion.

Diagnosis

The classical case in an endemic area should present no diagnostic difficulties. It is the occasional case in a non-maize eater that may present difficulties. A variety of erythemas and exfoliative skin lesions may mimic pellagra. The two characteristic features of cutaneous pellagra are its symmetrical distribution, determined by the clothes of the patient and exposure to sunlight, and the therapeutic response to nicotinic acid. A nutritional glossitis identical with the tongue changes seen in pellagra, may occur without the other signs of the disease. Pellagra may closely resemble sprue and, if the skin changes are minimal, the distinction between the two diseases may be difficult. The neurological signs may sometimes occur without any apparent involvement of the skin and digestive tract. In any unexplained delirium or amentia in a person who has been taking a poor diet for a prolonged period, the possibility of a pellagrous origin should be remembered.

Finally, there is a very rare familial inborn error of tryptophan metabolism which may closely mimic pellagra.

Prognosis

In the endemic areas the majority of patients are mild cases, improving in the winter and relapsing with the increased sunshine in the spring. The mental symptoms are perhaps the most serious feature and may be permanent. Occasionally a fulminating form develops, with fever and severe prostration which is often fatal. In the past most of the deaths arose from secondary infections (notably tuberculosis and dysentery) or from emaciation due to general dietary failure, intensified by the diarrhœa.

Treatment

Specific vitamin therapy.—For quick relief of these symptoms nicotinic acid or, preferably, nicotinamide is invaluable. Nicotinamide is to be preferred, partly for the theoretical reason that it is the form in which the vitamin is actually utilised in the body, but also because it does not cause the unpleasant flushing and burning sensations that often result from taking niacin. These sensations are harmless and transitory, but may alarm the patient. A suitable dose for either nicotinamide or nicotinic acid is 100 mg. 4-hourly by mouth, although a smaller dose is likely to be effective. The vitamin is very rapidly absorbed from the stomach, despite the most severe digestive disorders. There is therefore no indication for giving it by intravenous or intramuscular injection, although preparations can be obtained for this purpose. The immediate response to nicotinamide is usually dramatic ; within 24 hours the erythema of the skin largely disappears, the tongue becomes painless and pale and the diarrhœa ceases. Often there is also striking improvement in the patient's behaviour and attitude. But nicotinamide alone is usually insufficient to restore health, because of other associated deficiencies, notably of protein and other components of the vitamin B complex. The administration of yeast or yeast extract is a valuable aid to treatment.

Diet.—The first aim should be to compensate for the qualitative and quantitative deficiencies of the previous diet. If possible, the food should provide 100 to 150 g. of good protein, supplied by milk, eggs, meat or fish. Plenty of carbohydrate and fat is also desirable, sufficient to provide up to 3500 Cal./day, to restore the patient to normal weight. The food should be low in roughage at first in order to avoid further irritation to the inflamed intestines and consequent continued diarrhœa. When the diarrhœa ceases, fruits and green vegetables are useful for preventing the constipation that sometimes follows. The diet may be poorly tolerated at first, because the mental state of the patient may result in rebellion against the unaccustomed food. Furthermore, the sore mouth may make eating difficult, and extra food may temporarily intensify the diarrhœa.

General measures.—Rest in bed and sedation are necessary for severely ill pellagrins, especially those with marked mental symptoms ; they are often troublesome patients, so their behaviour must be tolerated with objective understanding of its cause. If the dermatitis is associated with much crusting or secondary infection, gentle washing with a dilute disinfectant solution is indicated. If the diarrhœa is severe enough to interfere with sleep or to cause electrolyte disturbances, preliminary treatment with tincture of opium should be given until it is brought under control with nicotinamide. The constipation that may follow later sometimes requires enemata for its relief.

Prevention

The dramatic disappearance of pellagra from the Southern States of the U.S.A. is clear proof that the disease can be prevented. Its disappearance has sometimes been attributed to the fortification of bread with nicotinic acid, but this is only one of several factors which have produced this satisfactory result. " The most likely reason is the general improvement in the economic state of the population " (Bean *et al.*, 1949) and it is " related to the many forces in the economic development of a people " (McLester & Darby, 1952).

From the standpoint of agricultural policy, it is clearly wise to avoid too much dependence on a single cereal crop, such as maize, or to devote too great an acreage of fertile land for the cultivation of cash-crops, such as cotton or tobacco. Animal husbandry should be encouraged in all areas where pellagra is endemic.

For the medical practitioner in such an area, without direct influence in matters of agricultural policy, the best advice that he can give to his patients is to take as much milk, eggs and meat as they can afford. He will also do well to prescribe yeast extract for the families of his pellagrous patients.

CHAPTER 35

KERATOMALACIA

DEFINITION

A DISEASE characterised by softening and necrosis of the cornea of the eye, often leading to ulceration, perforation, panophthalmitis and blindness.

Geographical distribution

The disease is important as a cause of blindness among Indians, Chinese, Indonesians and other rice-eating peoples of Asia ; it also occurs in parts of Africa. In Europe and America it is very rare, but an outbreak occurred among infants in Denmark during the First World War, when the dairy produce of that country was largely diverted to Germany. It occurs most commonly in children, though adult European prisoners in the Far East during the Second World War were sometimes affected.

Ætiology

The disease in man is very similar to the changes that arise in the eyes of animals as a result of long-standing deficiency of vitamin A. It only occurs in patients who have been living for long periods on diets almost entirely devoid of vitamin A. Early cases respond promptly to the administration of fish-liver oils rich in the vitamin.

In many parts of the East, xerophthalmia and other signs of vitamin A deficiency are extremely common ; yet keratomalacia is rare. This may be in part attributable to the fact that there are reserves of vitamin A in the liver which are only completely used up after a long period on diets totally devoid of the vitamin. Only when these reserves are gone is the cornea affected. Also, the disease may be precipitated by deficiencies of other nutrients such as protein and riboflavin. It is sometimes associated with kwashiorkor (Oomen, 1954) and with clinical signs attributable to deficiency of riboflavin and the B group of vitamins (Blumenthal, 1950).

Morbid anatomy and pathology

No systematic study of the morbid anatomy of the various stages of the disease appears to have been made in man. In animals with vitamin A deficiency there is keratinisation of the superficial layers of the cornea and degenerative changes in the basal layers in the advanced disease. In man the essential feature is a softening of the cornea, presumably due to a weakening of the collagen and mucopolysaccharides that compose it. The cornea is an avascular structure, and it is generally held that its cells derive their oxygen by diffusion from the atmosphere. Flavoproteins are an essential part of the mechanisms for making this oxygen available to the enzyme systems of the cells. The riboflavin necessary for the synthesis of these respiratory enzymes is likely to be supplied through the tears and the secretions of the meibomian glands which are especially rich in this vitamin (Philpot & Pirie, 1943; Pirie & van Heyningen, 1956). Vitamin A deficiency in animals leads to a blocking of the ducts of these glands with plugs of keratin. Thus experimental xerophthalmia in animals may be followed by an invasion of the cornea with blood vessels giving a microscopical appearance very similar to the appearance produced in experimental riboflavin deficiency (Bessey & Wolbach, 1939). In other words vitamin A deficiency may produce a secondary deficiency of riboflavin in the cornea. This effect would be aggravated by a primary deficiency of riboflavin affecting all the tissues.

Clinical features

The earliest manifestations are usually night blindness and xerophthalmia. These are danger signals, although usually they do not progress and the cornea is unaffected. Especially if there is deterioration in general health (associated with kwashiorkor, tuberculosis, cirrhosis of the liver or other chronic disease), the conjunctival condition spreads to the cornea which becomes dull, lustreless and eventually opaque. Later the cornea undergoes necrosis and ulceration. If untreated, the ulcer perforates and the eye is lost. In some patients keratomalacia may develop without any obvious xerophthalmia, especially if there are other signs suggesting riboflavin deficiency, *e.g.* multiple mucocutaneous degenerative changes as is shown in Plate XX, B (Blumenthal, 1950).

Diagnosis

This is usually easy. The condition may, however, be masked by coexistent trachoma; the two diseases sometimes occur together. Trachoma usually begins on the conjunctival surface of the upper lid and—when later it extends to the cornea—the opacity (pannus) comes down like a window-blind from above. Keratomalacia must also be distinguished from other diseases causing corneal opacities—notably congenital syphilis.

Prognosis

Keratomalacia is always a serious disorder, which threatens both life and sight. Unless early and adequate treatment is given, there is a grave risk of blindness or death from associated diseases. In many Eastern countries keratomalacia is at least as important as smallpox, syphilis and gonorrhœa in destroying the sight of children.

Treatment

In severe cases vitamin A, 75,000 i.u. daily, in the form of halibut-liver oil or some equally potent preparation by mouth, and riboflavin

5 mg. three times a day—also by mouth—are recommended. In early cases 10 ml. of cod-liver oil daily is usually sufficient to bring about a rapid and marked improvement. Injections of vitamins are seldom needed. Some antibiotic is essential to treat or prevent secondary infections in the eye. Local treatment of the eye is not necessary, unless there is already disorganisation, when the skilful services of an ophthalmic surgeon will be needed. General treatment of the patient is most important. A good all-round diet and attention to any associated infection is essential.

Prevention

Keratomalacia is usually associated with great poverty, famine and other circumstances over which it is difficult to have immediate control. Yet reports from Singapore (Williamson & Leong, 1949) and Indonesia (Oomen, 1954) show that keratomalacia may arise in the children of parents with incomes well above the poverty level. In Singapore there was an increase in keratomalacia attributed to increased sales of dried and condensed milks. The vitamin A content of such milks was determined and some samples had so little that an infant fed wholly on such proprietary milk preparations would get less than 400 i.u. of vitamin A daily. Such low intakes would certainly contribute to the production of keratomalacia. Most of these proprietary preparations were made from dried skimmed milk ; there may well be a case in some countries for legislation against their sale, unless it is made quite clear on the label that they are unsuitable for infants under 6 months of age. In other patients gross maternal ignorance of the essentials of infant feeding is the main cause. Whenever keratomalacia is common, the maternity and child health services must take the lead in organising preventive measures.

CHAPTER 36

NUTRITIONAL ANÆMIAS

INTRODUCTION

THE life of a red blood corpuscle is about 120 days. The bone marrow is continually making replacements at a rate which enables the total red cell population to be renewed every 3 to 4 months. This renewal requires the daily synthesis of 7 to 10 g. of hæmoglobin and the construction of the corpuscles to carry the pigment. For this synthesis a variety of materials is needed by the bone marrow, particularly certain minerals, vitamins and protein.

Minerals.—*Iron* is an essential component of hæmoglobin. In the absence of a sufficiency of this metal, the red blood corpuscles are small (microcytic) and inadequately supplied with hæmoglobin (hypochromic). Iron is absorbed mainly from the duodenum and jejunum.

Although iron salts have been given for a variety of illnesses from the time of Hippocrates (born 460 B.C.), it was not until 1681 that they were introduced to clinical medicine for the treatment of anæmia by Sydenham, who administered 'iron and steel filings steeped in cold Rhenish wine.' One hundred and fifty years were to elapse before Blaud (1831) recognised the nutritional nature of anæmia and emphasised the specific action of iron in its treatment, for which purpose he prescribed a preparation of ferrous iron in adequate doses.

Copper and *cobalt* have been shown to be necessary in very small amounts for the formation of red blood corpuscles in several species of animals and by inference in man. However, anæmia attributable to copper or cobalt deficiency has seldom, if ever, been satisfactorily demonstrated in man, though such anæmias are important in veterinary practice.

Vitamins.—Both *vitamin* B_{12} and *folic acid* are intimately concerned with metabolism, particularly of nucleic acids, and they are necessary for the normal development of the blood cells in the bone marrow, and also probably for every cell in the body. While folic acid is absorbed mainly from the jejunum, vitamin B_{12} is absorbed from the ileum and especially from its terminal portion. This information is of considerable diagnostic value. In the absence of an adequate supply of these factors, megaloblastic blood formation occurs (p. 239).

Ascorbic acid is also concerned in blood formation since anæmia in scurvy usually responds to the administration of this vitamin alone. Moreover, there is evidence that ascorbic acid plays a part in the absorption of iron and perhaps also in the metabolism of folic acid.

Pyridoxine is also required for hæmoglobin formation. Anæmia responding to pyridoxine therapy has been discussed on page 247. It is extremely rare in human beings.

A deficiency of nicotinic acid and riboflavin can produce anæmia in animals, but there is no satisfactory evidence that they do so in man. The anæmia of pellagra is due to associated deficiencies. Thiamine, inosital and pantothenic acid have not been shown to be necessary for blood formation in man.

Protein.—Protein deficiency may be an important contributory cause of nutritional anæmia. The factors concerned are an increase in the plasma volume and reduced metabolism of the bone marrow. In addition, the production of the protein portion of the stroma framework of the red corpuscles and the synthesis of globin will be affected by a diminished intake of amino acids. However, the deficiency must be severe and long continued because the protein requirement for the synthesis of hæmoglobin takes precedence over that required for the manufacture of serum proteins. One of the most important factors causing the macrocytic anæmia associated with cirrhosis of the liver of nutritional origin is protein deficiency. The anæmia is characterised by large flat cells and a normoblastic marrow. The anæmia of protein deficiency, as seen in the most classical disease due to protein deficiency, namely kwashiorkor, is discussed on page 404.

In this chapter only anæmias primarily nutritional in origin are described. Anæmia associated with chronic bleeding, hookworm infection and other diseases is discussed in Chapter 43.

THE ANÆMIA OF IRON DEFICIENCY

Iron deficiency is by far the most common cause of anæmia in every part of the world at the present time. In Great Britain alone, very large numbers of people suffer from varying degrees of iron deficiency anæmia. About 85 per cent. of the anæmias encountered among rural labourers in hot, damp, tropical regions respond to iron therapy (Foy & Kondi, 1957).

Since a remarkable improvement in health, happiness and efficiency can be quickly and cheaply obtained if the condition is recognised and correctly treated, it is important to know the causes of the disease, the type of individual who is particularly liable to develop it and the appropriate measures for its prevention and treatment.

The subject of iron deficiency anæmia with special reference to its ætiology, prevention and treatment in the tropics is discussed in detail in a World Health Organization report (1959).

CHRONIC NUTRITIONAL HYPOCHROMIC ANÆMIA

This name was suggested by Davidson and Fullerton (1938) because it indicates that the anæmia concerned is a chronic condition which starts insidiously, that its cause lies in the failure of the diet to meet the patient's requirements, and that the essential feature of the blood picture is hypochromia of the red cells, evidence of iron deficiency. It is an extremely common disorder all over the world; in Europe and North America it occurs almost exclusively in two vulnerable groups, namely women of the child-bearing age and in infants and young children. This is clearly illustrated in Fig. 36, 1 from the paper by Davidson and Fullerton dealing with the incidence of anæmia in a sample population of 3000 persons comprising both sexes and all ages from infants to old people. This figure based on data collected more than 25 years ago still gives a true picture of the age and sex incidence of iron deficiency anæmia at the present time. Iron deficiency anæmia in males in Great Britain is seldom due primarily to nutritional causes and the diagnosis of chronic nutritional hypochromic anæmia should never be made in men unless all sources of pathological blood loss and organic disease have been excluded.

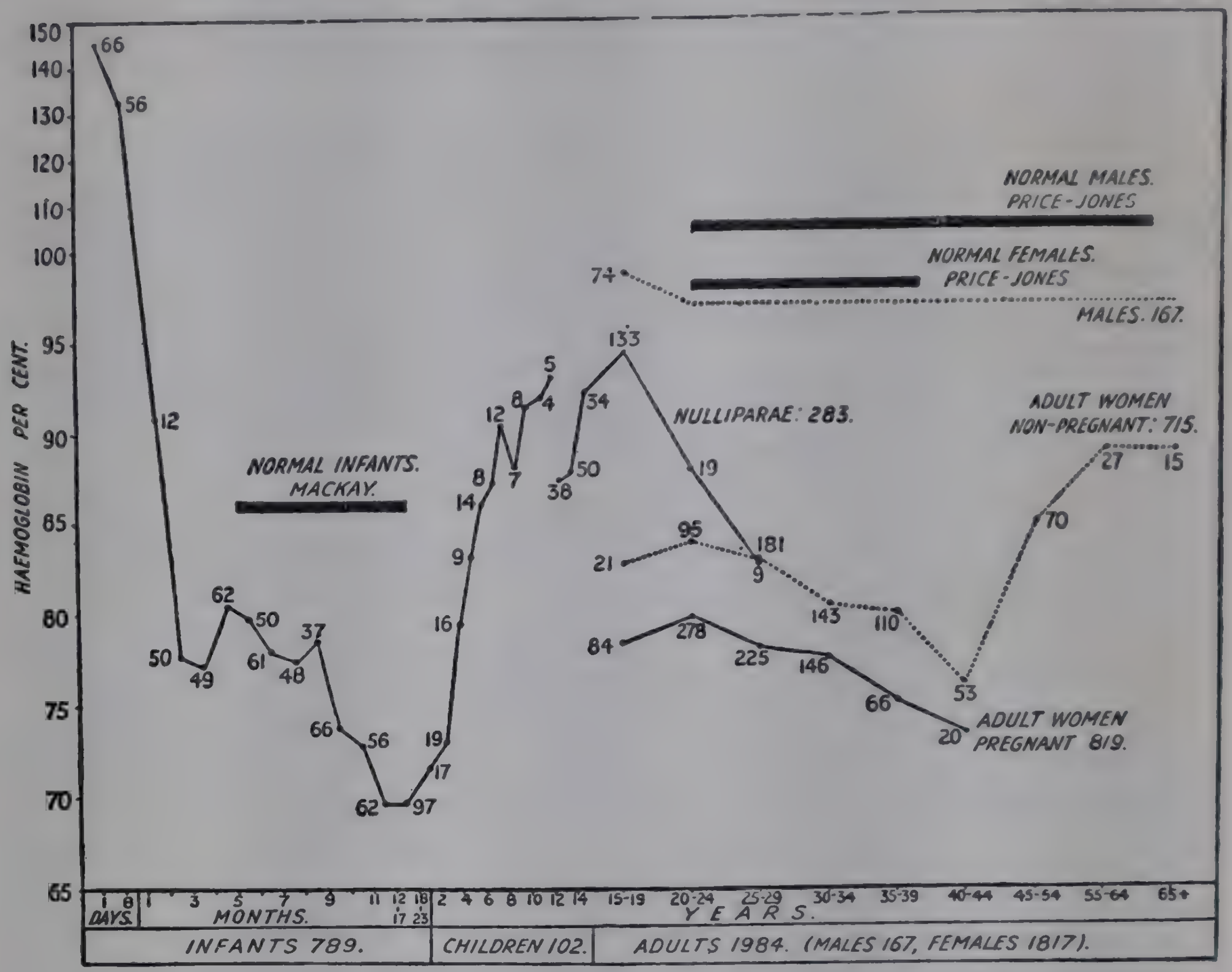


FIG. 36, 1. Chart showing average hæmoglobin levels among poor people of all ages and both sexes.

WOMEN OF THE CHILD-BEARING AGE

Ætiology

The factors concerned are dietary deficiency, defective absorption and, most important of all, increased needs for iron which are the direct consequence of menstruation and pregnancy.

Intake.—In Great Britain the diet of poor people has contained marginal amounts of iron for almost a century. Fullerton (1936) estimated the average iron intake of poor people in Aberdeen as only 7·5 mg./day. Although nutritional standards have greatly improved since then, there are still a large number of families in Great Britain whose diet is insufficient in its total content of iron.

A similar problem, though more severe, exists in many underdeveloped countries throughout the world.

Some poor people, living on whole-grain cereals (especially millets), have intakes of iron that compare favourably with the allowances recommended in Great Britain and the U.S.A. (Chapter 15). In many regions of India the average daily intake of iron is stated to be 20 to 40 mg. ; yet iron deficiency anæmia is still very common in these regions. The explanation is that there are many factors which can interfere with the absorption and utilisation of iron, as described below.

Absorption.—In Chapter 11 it has been explained that phytic acid and other phosphates inhibit iron absorption, whereas ascorbic acid, calcium and protein facilitate it. It is thus easy to understand why poor diets, such as those composed mainly of millet, though often apparently adequate in regard to their total iron content, can nevertheless result in iron deficiency anæmia among their consumers.

Diseases affecting intestinal absorption, such as the malabsorption syndrome (p. 508), may result in conditioned iron deficiency.

ACHLORHYDRIA is present in at least 75 per cent. of women suffering from severe nutritional hypochromic anæmia in Great Britain. The cause of achlorhydria and its significance is disputed (p. 176). Hydrochloric acid and pepsin facilitate the liberation of iron in the ferrous state from its bound complex forms in food, and the lowering of the *p*H of the contents of the small intestine is of importance in helping absorption. The fact that anæmic patients with achlorhydria respond excellently to the daily administration of preparations of medicinal iron containing 150 to 200 mg. of a ferrous salt in no way invalidates the above statements, which are concerned with the absorption of iron from a diet containing only 10 to 15 mg. or less Fe/day. Although the effects of achlorhydria on the liberation of iron from food and its absorption may not be of much importance to males whose requirements for iron are low, they may play a significant part in the production of anæmia in women of child-bearing age whose requirements for iron may be high. Gastric operations (*e.g.* complete or partial gastrectomy ; gastroenterostomy) frequently lead to the development of iron deficiency anæmia. Defective absorption of iron occurs partly as a result of the achlorhydria produced and partly from small intestinal hurry.

Increased needs.—During reproductive life there are extra demands for iron which have to be met from the diet.

MENSTRUATION.—The amount of blood lost in a normal menstrual period varies very much from one woman to another. A healthy woman may lose 30 mg. Fe at each period, but the losses may be as much as

120 mg. Fe in anæmic women (Barer & Fowler, 1936). In other words, every woman of the child-bearing age requires to absorb at least 1 mg. Fe/day and often considerably more in addition to 1 mg. needed to replace normal losses from the gut and urinary tract.

Pregnancy and lactation.—The loss of iron involved in a normal pregnancy (iron content of fœtus, 400 mg.), delivery (iron content of placenta, uterus and blood loss, 325 mg.) and lactation (iron content of milk during 6 months of lactation, 175 mg.) may total approximately 900 mg. This entails an extra demand of approximately 2 mg. Fe/day for a period of 460 days.

It is obvious that menstruation and pregnancy greatly increase a woman's requirements for iron ; it is not surprising that diet alone is often unable to meet the deficit.

Clinical features

Nutritional anæmias all arise slowly and take months or years to develop. During this time the body is capable of making considerable adjustments to the reduced oxygen-carrying capacity of the blood. Thus it is not unusual to find a woman undertaking her normal housework with a hæmoglobin level of less than 7·5 g./100 ml. (50 per cent.). Such a degree of anæmia arising from sudden hæmorrhage would be fatal. Low levels of hæmoglobin are, of course, always associated with a feeling of lassitude and an inability to make sustained physical effort ; but these symptoms may be attributed by the patient to other causes.

Anæmic patients suffer from a group of clinical features which are the direct result of the diminished oxygen-carrying power of the blood on the tissues and organs of the body. The occurrence and the severity of these features are dependent on the degree of anæmia, and especially on the rapidity of its development, but they are similar in all types of anæmia. It is therefore essential to realise that the diagnosis of the *type of anæmia* cannot be made on clinical grounds alone but only after examination of the blood. The clinical features of anæmia are : general fatigue and lassitude, breathlessness on exertion, giddiness, dimness of vision, headache, insomnia, pallor of the skin and, much more important for diagnosis, of mucous membranes, palpitation, tachycardia, cardiac dilatation, functional systolic murmurs, anorexia and dyspepsia, tingling and ‘ pins and needles ’ in the fingers and toes (paræsthesiæ), angina pectoris (due to myocardial anoxæmia), especially in older patients with coronary sclerosis. In severe cases there may be some œdema of the ankles and crepitations at the bases of the lungs ; in addition to the general features of anæmia described above there are other signs of nutritional deficiency, particularly glossitis, angular stomatitis, koilonychia and dysphagia. The glossitis is usually referred to as chronic atrophic glossitis because atrophy of the papillæ and mucous membrane gives the tongue a smooth glazed appearance. The atrophy begins at the edges and later affects the whole tongue. As a result the tongue appears moist and exceptionally clean. Koilonychia is the name given to certain changes in the nails ; first there is brittleness and dryness : later there is flattening and thinning and finally concavity (spoon-shaped nails). Dysphagia occurs occasionally in severe cases (p. 486). In a small proportion of severe long-standing cases the spleen may be palpable. Hypochlorhydria or achlorhydria is commonly present. While paræsthesiæ are common, objective signs of disease of the central nervous system are never found.

In nutritional hypochromic anæmia blood examination shows a hypochromic, microcytic anæmia. The hæmoglobin level commonly lies between 4·5 and 9 g./100 ml. (30 and 60 per cent.), and the red cell count between 3 and 4·5 million, with a mean corpuscular hæmoglobin concentration of about 25 (normal 32–38 g./100 ml.) and a mean corpuscular volume of about 65 (normal 80–100 cu. μ). The total and differential white cell counts show little change from normal. The bone marrow shows a normoblastic reaction.

Tasker (1959) has shown that in patients with chronic nutritional anæmia in Malaya there is a decrease in the blood volume although the plasma volume remains constant. This may lead to an underestimation of the severity of the anæmia, because the total circulating hæmoglobin is reduced more than the hæmoglobin concentration as measured in whole blood.

Course and prognosis

The anæmia is often well advanced, *e.g.* hæmoglobin level 7·5 g./100 ml. (50 per cent.), before significant symptoms are apparent. If untreated the condition follows a chronic course. The importance of the syndrome is not that it is dangerous to life but that it leads to a loss of efficiency and impaired general health.

Prophylaxis and treatment

For the prophylaxis of iron deficiency anæmia in women, the greengrocer and the butcher are of particular importance. Once anæmia has developed it is to the chemist that one should turn for help. Every doctor must have some knowledge of the iron content of foods (see Table 11, 6) so that he may give sensible advice not only on which foods are of particular value in this respect but also in regard to their desirability as cheap sources of iron. Attention is directed to the fact that on both grounds the following articles of food can be recommended—oatmeal, peas and beans, and bread made from 85 per cent. extraction flour. Most green vegetables consumed in Europe are poor sources of iron. Those rich in iron, such as watercress and spinach, are only eaten occasionally and then usually in small amounts. Green vegetables, however, are of value in the prophylaxis of anæmia because they are rich sources of ascorbic acid which plays a significant role in the absorption of iron. Meat and eggs are valuable but relatively expensive sources of iron and should be eaten at least once daily. As already mentioned milk is a poor source of dietary iron. Women with heavy menstrual periods or who have repeated pregnancies usually require medicinal iron for prophylactic maintenance purposes as well as for treatment.

Once anæmia has developed it is both unwise and uneconomic to try and correct it by dietary means alone. In one clinical experiment, carried out by one of us (S. D.) over 25 years ago, a group of severely anæmic poor women were given a diet rich in animal protein and other expensive foods known to be good sources of iron for a period of 30 days. The mean rise in hæmoglobin level was approximately 5 per cent. The women were then given one 0·2 g. (3 gr.) tablet of ferrous sulphate containing 60 mg. of elemental iron thrice daily for 30 days. The total cost of the medicinal iron therapy for this period was approximately three shillings, which was less than the cost of the dietary supplement of iron-rich foods for one day, while the mean rise in hæmoglobin level was 30 per cent.

The administration of hydrochloric acid is of no value in improving absorption of iron. Provided the patient is taking a well-balanced diet, the prescription of vitamin preparations is unnecessary and wasteful. Only if the history and the clinical examination suggest the presence of scurvy should a supplement of ascorbic acid be given. The administration of trace elements (copper, cobalt, molybdenum, manganese) is also, of no value.

Oral therapy.—Provided inhibitory factors such as sepsis, toxæmia or hæmorrhage are absent, the administration of iron should lead to a rise of at least 1 per cent. per day in the hæmoglobin level. Ferrous sulphate is the preparation of choice. The dose is 0·2 g. (3 gr.) in tablets three times a day. A bottle of 100 tablets will last a month. Ferrous gluconate, ferrous succinate and ferrous fumarate are equally effective, but more expensive. For the exceptional patient who is unable to swallow tablets, Ferrus Sulphate Mixture N.F. should be prescribed. One tablespoonful of this mixture is the equivalent in iron content of one tablet of ferrous sulphate.

Gastrointestinal upsets and other indications of intolerance of iron have been commonly reported, but controlled trials (Kerr & Davidson, 1958*a*) have indicated that these are mainly psychological in origin.

Treatment should be continued for at least one month after the hæmoglobin level has returned to normal in order to restock the depleted body stores. In women past the menopause, recurrence is unlikely, but women who are still menstruating or who become pregnant may relapse and require regular checks on their level of hæmoglobin.

Prophylaxis in pregnancy.—Although in Great Britain severe anæmia in pregnancy is rare, mild anæmia is common (Kerr & Davidson, 1958*b*). We recommend routine estimation of the hæmoglobin level in all women at their first antenatal visit. Those with a hæmoglobin level below 12·6 g./100 ml. (85 per cent.) should have iron therapy. Mild anæmia is so common in the third trimester that routine administration of iron to all patients from the twenty-fourth week to term is advised. The recommended preparation is ferrous sulphate and the dose is one tablet of 0·2 g. (3 gr.) thrice daily after food. Only if intolerance to ferrous sulphate is clearly demonstrated should the more expensive proprietary preparations of iron be prescribed.

Intravenous and intramuscular iron.—Rarely oral iron therapy is unsatisfactory ; then iron may be given parenterally. Several satisfactory preparations are on the market.

INFANTS AND YOUNG CHILDREN

Ætiology

The factors concerned with the production of iron deficiency anæmia in infants and young children may be summarised as follows.

1. **Inadequate stores of iron.**—(*a*) Milk is a poor source of iron and during the first 3 or 4 months, iron from dietary sources is scarcely used at all—indeed iron obtained via the placenta is the main source of iron for hæmoglobin synthesis in the infant's bone marrow for most of the first year of life. Thus it is very important that pregnant women should receive a well-balanced diet which contains at least 15 mg. Fe/day, and in addition the supplement of iron recommended above during the last trimester of pregnancy.

(*b*) The stores of iron derived from the physiological hæmolysis of red cells which occurs during the first few weeks of life play a very important part in preventing the onset of anæmia in infants. The newborn infant has a high red cell count and hæmoglobin level, presumably as a physiological adjustment to the limited oxygen supply which the placenta is able to provide in the last weeks of intra-uterine life. The excess red blood corpuscles are destroyed in the first few weeks after birth, sometimes producing a transient jaundice. The iron liberated by this hæmolysis is stored especially in the liver, spleen and bone marrow and is subsequently used again for the synthesis of hæmoglobin as the volume of blood increases with the growth of the child.

Premature infants naturally have a smaller red cell population—and hence a smaller store of iron after birth from this source—than do full-time infants. They are, therefore, particularly prone to develop anæmia if the measures discussed below for its prevention are not put into operation.

2. **Growth.**—Adequate supplies of iron to enable the bone marrow to manufacture the hæmoglobin required for the rapidly expanding blood volume of the actively growing infant or child are essential, otherwise anæmia is liable to develop. In the first year these supplies are mostly derived from the mother, as discussed above. If they prove inadequate, medicinal iron must be administered.

A normal newborn infant has about 0·5 g. Fe in his body ; in order to reach 5 g. by the age of 20, he must retain on average 0·6 mg. Fe/day throughout growth.

3. **Infections.**—Hæmopoiesis in infants and young children is depressed by infections to a much greater degree than is the case in adults. Metabolism of iron is interfered with by infections in a manner not fully understood. In addition, infections may lead to the dietary intake of iron being reduced because of loss of appetite, nausea or vomiting, and when diarrhœa is also present, impairment of absorption of iron results.

4. **Diet.**—Milk, the natural and principal food of infants during the first year of life, unfortunately has a low content of iron. For this reason nature has provided infants with additional sources of iron derived from the mother and from the physiological hæmolysis of the infant's red cells as described above.

Clinical features

In infants the symptoms of anæmia are not so easily recognised as in adults, but undoubtedly anæmia leads to impairment of general health and vitality.

Prevention

The prophylactic measures may be summarised as follows :—

1. The prevention and treatment of iron deficiency anæmia in pregnant women.
2. Efficient treatment of infections in infants.
3. The correction and treatment of factors causing blood loss in infants.
4. The provision of supplementary feeds of broth, egg yolk, vegetable purées, cereals and other easily digested sources of iron from the age of 4 to 6 months upwards.
5. The administration of prophylactic doses of iron to infants of low birth weight from the third month of life onwards.

Treatment and prophylaxis with iron

Once anæmia has developed, dietetic measures cannot be relied on to cure the anæmia and hence must be supplemented by the administration of medicinal iron. For this purpose iron and ammonium citrate or ferrous sulphate in solution is recommended.

For a child of 3 to 6 months, 0·2 g. (3 gr.) of iron and ammonium citrate in water sweetened with glycerin, three times a day, is a satisfactory preparation for prophylactic use. The dose should be 0·3 g. (5 gr.) three times a day if anæmia has already developed. For children of 6 to 18 months the prophylactic dose is 0·3 g. (5 gr.), while the curative dose varies from 0·6 to 0·9 g. (10 to 15 gr.) thrice daily. Ferrous salts of iron are equally efficacious in a dose approximately $\frac{1}{6}$ of that recommended for iron and ammonium citrate. Their efficiency is rapidly reduced if oxidation to the ferric state occurs. Accordingly they must not be prescribed in simple watery solutions but should be mixed with 50 per cent. glucose, which retards oxidation. Ferrous sulphate mixture for infants, N.F. is a suitable preparation for the treatment of anæmia in infants and young children and can be added to the milk in the feeding bottle. One teaspoonful containing 12 mg. of elemental iron is the usual dose.

NUTRITIONAL MEGALOBLASTIC ANÆMIA

This name is preferable to ' tropical megaloblastic anæmia ' since the disorder has been described not only in tropical countries but also, though rarely, in temperate climates. To Dr Lucy Wills must be credited the pioneer observations in 1931, which focused attention on this form of megaloblastic anæmia (p. 243).

ADULTS

The original cases reported by Wills were pregnant Indian women who had subsisted on extremely poor diets consisting mainly of rice, and seriously deficient in animal protein, minerals and vitamins. The disease also occurs in males but is much less common. Pregnancy is frequently associated with this disease, perhaps because it creates an increased demand for blood-forming nutrients.

Ætiology

The usual factors are a dietary deficiency of folic acid, protein and ascorbic acid resulting from poverty, religious tenets and other causes. The disease is most frequently found in vegetarians. Infections, particularly malaria and dysentery, often appear to play a part. Hindu women in cities like Bombay and Calcutta are particularly affected. In South Africa and in Fiji the disease is most frequently found in the Indian population.

Recent studies of megaloblastic anæmia using the modern techniques of microbiological assay and the absorption of radioactive B_{12} have been carried out in India and Africa. It is now certain that megaloblastic anæmias due to a deficiency of vitamin B_{12}, resulting either from direct dietary deficiency or from a lack of intrinsic factor, are not so uncommon as was previously thought (Metz *et al.*, 1962).

Clinical and hæmatological features

Like chronic nutritional hypochromic anæmia the disease progresses slowly : clinically the two diseases are indistinguishable in the early stages. In all countries nutritional megaloblastic anæmia is much less common than nutritional hypochromic anæmia. However, if untreated, the hæmoglobin is likely to fall to very low levels (2 to 4 g./100 ml.). Loss of weight and signs of various vitamin deficiencies are frequently but not always observed. Glossitis is often present. Paræsthesia is a common complaint ; it is doubtful whether subacute combined degeneration of the cord ever occurs. This is perhaps not surprising as deficiency of vitamin B_{12} is not believed to be an important factor in the production of this form of megaloblastic anæmia. In patients who are seriously ill, irregular fever is usually present.

The hæmatological features of the peripheral blood and bone marrow are the same as those described below for the disorder occurring in infants.

Differential diagnosis

While the features of the anæmia are similar to those of Addisonian anæmia there are certain characteristics which may help to distinguish the two conditions. In nutritional megaloblastic anæmia the patients are usually younger. Free hydrochloric acid is often found in the gastric juice. The history of a very poor diet is characteristic. Autolysed yeast (Marmite), crude liver extracts (by mouth or injection), or folic acid usually elicits a response in the bone marrow with the production of new red cells ; but the response is frequently inadequate or absent to amounts of refined liver extract or vitamin B_{12} which would be effective in Addisonian anæmia. It is now believed that the blood-forming properties of autolysed yeast (' Wills' factor ') and of crude liver extracts is due, in part at least, to their content of folic acid, though some other unknown factor or factors may also be concerned.

The differential diagnosis between nutritional megaloblastic anæmia in a pregnant woman and the megaloblastic anæmia of pregnancy is difficult and may even be impossible. In the former disease a history of severe dietary deficiency is a predominant feature which is often absent in the latter. Nutritional megaloblastic anæmia is sometimes accompanied by diarrhœa, and when this is the case it is doubtful if the disease can be distinguished from the conditioned megaloblastic anæmia due to the malabsorption syndrome. This is particularly so in the cases of ' sprue ' reported from the West Indies and tropical America (Spies *et al.*, 1946), which differed from Asiatic sprue in various ways, notably in respect of the lower social class of the patients and the presence of severe malnutrition.

Course and prognosis

Without adequate treatment there is a high mortality. This was reduced by Wills' discovery of the value of yeast extracts. Yet many patients failed to respond to yeast and simple dietary measures. With the introduction of folic acid and the realisation of the value of blood transfusions, the outlook is now completely changed and with proper treatment deaths should be very rare.

Treatment

Folic acid is undoubtedly the drug of choice. A dose of 10 to 20 mg. daily is usually effective. For the exceptional case shown to be due to a deficiency of vitamin B_{12}, cyanocobalamin in the dosage recommended for pernicious anæmia (p. 242) should be given. Patients who are seriously ill (hæmoglobin level less than 5 g./100 ml.—30 per cent.) will generally need blood transfusion to tide them over until the folic acid has acted. It goes without saying that the treatment of all nutritional megaloblastic anæmias requires in addition a well-balanced diet providing ample calories, minerals, vitamins and especially, perhaps, proteins. If such a diet can be maintained after the patient has recovered, further treatment with folic acid or vitamin B_{12} will be unnecessary; but the patient may not be able to afford such a diet. A follow-up clinic is therefore invaluable for detecting relapses in their earliest stages and correcting them by a return to medication, and also for periodic dietetic advice which can help to prevent a return to the grossly defective diet that was chiefly responsible for the onset of the disease.

INFANTS AND YOUNG CHILDREN

Primary nutritional megaloblastic anæmia in infants is certainly a very rare disease in Great Britain. S. D. has seen only one such case. In the U.S.A., Zuelzer and Ogben (1946) reported twenty-five cases. Most of the infants were severely anæmic and five had hæmoglobin levels below 4 g./100 ml. Many had been fed on artificial infant foods which were unsatisfactory in their content of protein, ascorbic acid and folic acid; five of the children suffered from scurvy. Six of the mothers suffered from anæmia. Manufacturers in the U.S.A. have since ensured that all dried milk for infants contains adequate ascorbic acid, and consequently the disease has largely disappeared in that country. In Germany and in Italy megaloblastic anæmia in children has also been reported (Wintrobe, 1956), especially in infants fed exclusively on goats' milk. Infections, particularly gastrointestinal diseases, are frequently present.

Until recently the disease has not been mentioned in textbooks of tropical medicine and was generally considered to be rare in all parts of the world. With the widespread use of marrow biopsy as a means of diagnosis, it has now become clear that the disease is not uncommon in the tropics. In a study of the bone marrow in fifty children in Indonesia suffering from kwashiorkor, Lien-Keng, Poesponegoro and Seng Hin (1957) found a megaloblastic marrow in five of them. Megaloblastic anæmia has also been found to occur in severely malnourished children in Durban, South Africa, and in Jamaica—indeed it is probably a feature of severe cases of kwashiorkor, which has been overlooked in the past.

Clinical and hæmatological features

These do not differ from those of any other anæmia in childhood; the degree of anæmia may be very severe. A red cell count of under 1·5 million with a hæmoglobin less than 5 g./100 ml. (30 per cent.) may be found. The megaloblastic appearance of the bone marrow is indistinguishable from that of classical Addisonian pernicious anæmia. This is also the case in regard to the peripheral blood picture in some children. In others, however, in which there is a dual deficiency of iron and folic acid (dimorphic anæmia) the values for the colour index and the mean corpuscular volume are normal or even slightly less than normal. Then diagnosis can only be made with certainty by examination of a specimen of bone marrow. Marrow biopsy should be undertaken in any infant suspected of having this type of anæmia because of the vital importance of correct and early diagnosis.

Treatment

The disease generally responds to folic acid, but progress may be slow and blood transfusions are sometimes needed.

Anæmia due to Subnutrition and Starvation

Patients who have lost weight from a simple insufficiency of food are often mildly anæmic. In the Minnesota experiment (Keys *et al.*, 1950) volunteers lived for 24 weeks on an inadequate diet and lost about 25 per cent. of their body weight ; the hæmoglobin level was reduced to an average value of 11·7 g./100 ml. (78 per cent.) and the red cell count to 3·78 million/c.mm. Their red blood corpuscles were normal in size and contained a normal amount of hæmoglobin. The cause of their anæmia is that all the organs of the body—with the exception of the skeleton and nervous system—shrink when the body is short of calories, yet the total volume of water in the body is little changed. The red cell population, or ‘ erythron,’ is no exception. So one effect of weight loss from lack of calories is a smaller red cell population in a normal plasma volume. If the patient has lost 25 per cent. of his normal lean body weight, the hæmoglobin concentration in his blood is likely to be 75 per cent. of normal.

Nutritional Anæmias of Mixed Ætiology

It is understandable that there are certain situations in which deficiency of iron and of folic acid or vitamin B_{12} coexist. Thus a dual deficiency of iron and folic acid is usually present in the megaloblastic anæmias of pregnancy, malabsorption and malnutrition. In order to determine the nature of the anæmia prevalent in a given area, and thus the most economical means of treating and preventing it, a preliminary survey by a trained hæmatologist, using modern techniques, is an invaluable initial step.

Nutritional Anæmia in Tropical Countries

From what has been said it must be clear that anæmia, especially the type due to iron deficiency, is extremely common and causes a vast amount of ill-health and a great loss of working capacity and economic efficiency in all temperate climates even when the economic state of the people is good. In underdeveloped tropical countries nutritional anæmias occur even more frequently and are more severe in degree. The basic causes of the different types of anæmia in tropical countries, their clinical features and their treatment, are similar to those occurring in temperate climates and as these matters have already been discussed there is no need to repeat them. There are, however, certain factors in tropical countries which are not present in temperate climates and which require consideration. Thus, in tropical countries the demands for iron may be greatly increased by the loss of hæmoglobin in the fæces and urine resulting from hæmorrhage due to *parasitic diseases* such as ankylostomiasis and to a lesser extent schistosomiasis. In addition significant amounts of iron may be lost daily in the sweat and shed epithelial skin cells when work is undertaken in hot climates. When these additional factors operate in persons who are already partaking of diets which may be gravely deficient in iron and protein, it is not surprising that iron deficiency anæmia in tropical countries is both frequent and severe. The incidence and pathogenesis of nutritional anæmias in tropical countries has been reviewed in detail by Woodruff (1961).

The nutritional megaloblastic anæmias of tropical climates are always associated with diets poor in animal protein and rich in carbohydrate, and hence low in vitamin B_{12} and folic acid. The role of *protein malnutrition* in the causation of tropical nutritional anæmia has been extensively studied in the disease kwashiorkor which is primarily due to protein deficiency. The anæmia is usually mild or moderate in degree and is normocytic or slightly macrocytic with a normoblastic bone marrow. However, when parasitic infections are present, as is frequently the case, or when protein deficiency in the diet is augmented by a failure in protein synthesis by a diseased liver, or when the intake of essential hæmatinics such as iron, ascorbic acid, vitamin B_{12} and folic acid, is poor, the resultant anæmia in kwashiorkor may be severe in degree and may be of the hypochromic type, the megaloblastic type or a mixed type, giving the peripheral blood picture described as dimorphic by Trowell (1943).

Correction of the anæmia of protein malnutrition of short duration, as occurs in infants, may be rapid, but in adult life if it has been present for a long time, many months of treatment with a high protein diet together with such hæmatinics as are required may be needed before the blood is restored to normal.

OTHER ANÆMIAS

The anæmias of scurvy and pyridoxine deficiency are discussed on pages 217 and 247 respectively.

CHAPTER 37

LESSER NUTRITIONAL DISORDERS

CONDITIONS FREQUENTLY ASSOCIATED WITH A DEFECTIVE DIET

IN this chapter an account is given of a variety of clinical conditions which are commonly found in malnourished people. For the most part they do not result in severe disability and are rarely a primary cause of complaint. They are usually found on the routine examination of school children, the medical inspection of a labour force, or at maternity and child-welfare clinics.

Much has been written about the ætiology of each of these conditions. In general it may be said that the majority can arise from a variety of causes both dietary and otherwise. The practical importance of these stigmata is that their presence, either in an individual or in a community, should *at once draw attention to the diet.* It is primarily for this reason that they have been included in this chapter. An accurate diagnosis of the cause of these conditions can only be made by careful epidemiological studies and by the results of appropriate therapeutic trials.

DISORDERS OF THE SKIN

Follicular keratosis

The normal human skin contains pores, which are the openings of microscopic follicles. The secretions of the sebaceous and sweat-producing glands enter the follicles and reach the surface through the pores. Hairs emerge from their roots through the same follicles. In follicular keratosis the follicles become blocked with plugs of keratin derived from their epithelial lining which has undergone squamous metaplasia. This pathological change is characteristic of vitamin A deficiency (Chapter 13). Therapeutic trials in many parts of the East and in Africa have repeatedly shown that halibut-liver oil, red palm oil or other oils rich in vitamin A or carotene may produce a striking clinical improvement in follicular keratosis ; yet other factors may contribute to its development, such as exposure to sunlight, lack of cleanliness and deficiency of essential fatty acids and pyridoxine (Chowdury *et al.*, 1954). Certainly follicular keratosis was not a regular feature in experimentally induced vitamin A deficiency in British adults (Hume & Krebs, 1949). Possibly it requires many years of chronic vitamin A deficiency before sufficient keratin accumulates to produce the characteristic horny plugs. A further difficulty is that slight follicular keratosis is not uncommon in British people who are adequately nourished in respect of vitamin A. Thus follicular keratosis is not a specific or constant feature of vitamin A deficiency. Yet it is useful to recognise it and record its incidence in the course of clinical nutrition surveys, since it may help to confirm a dietary history suggesting deficiency in the diet.

The typical distribution of follicular keratosis is over the backs of the upper arms and the fronts of the thighs, but it may extend over the buttocks and indeed over the whole trunk. Only the feet, hands and face may be spared. Some degree of xeroderma (see below) is commonly associated. The horny plugs that project from the follicular orifices can often be pulled out with a fine pair of forceps ; they give the skin a characteristic feeling of roughness, like that of a nutmeg grater. Because of its appearance, the condition has been called ‘ toad-skin ’ or phrynoderma. The appearance is distinct from the condition sometimes seen in scurvy, in which the hyperkeratosis is superficial and perifollicular—often with a small underlying hæmorrhage—but without any projecting horny plug (Chapter 31). Plate XIX, A, shows the clinical features of follicular keratosis, and Plate XIX, C, the histological structure.

Folliculosis is sometimes mistaken for follicular keratosis. The follicles are raised above the surface, giving a superficial appearance of chronic ‘ gooseflesh.’ But no horny plug projects from the follicular orifices. It is common on the backs of the arms of well-nourished British school children, and although its cause is unknown, there is no evidence that it has any nutritional significance.

Xeroderma

This means dryness of the skin. Instead of the normal smooth, moist, velvet texture, the skin feels dry and often rough. On uncovering the legs, a cloud of fine, branny dandruff is often seen. Xeroderma is commonly but not constantly associated with follicular keratosis and ‘ crackled skin.’

‘ Crackled skin ’

In this condition—also called ‘ crazy-paving skin ’—the appearance suggests a layer of lacquer painted on the surface, which on drying has broken up into individual islands of varying size. There is often some desquamation from the borders of each island, while the intervening gaps may become fissured, infected and lead to ulceration. The commonest site for this lesion is the shins, and it seems probable that exposure to dirt and alternate heat and moisture often contributes to its causation.

Pachyderma (‘ Elephant skin ’)

This word was introduced by Nelson (1953) to describe a condition common in malnourished people. The areas of skin affected are thick, rough and thrown into folds like the skin of an elephant (Plate XIX, D). The usual sites are the back of the forearm immediately below the elbow, the front of the leg immediately below the knee, and across the instep of the foot. These are sites where dirt easily accumulates.

It is obviously unwise to suggest that ‘ elephant skin,’ ‘ crackled skin ’ and xeroderma are due solely to poor nutrition. On the other hand Nicol (1949) has demonstrated their probable nutritional significance by showing that these conditions are less common among Nigerians who eat red palm oil (rich in vitamin A activity) than among those who do not.

Dyssebacea (nasolabial seborrhœa)

This term has been given to the appearance of enlarged follicles around the sides of the nose and sometimes extending over the cheeks and forehead. The follicles are plugged with dry sebaceous material which often has a yellow colour, for which reason Stannus originally coined the name ‘ sulphur flake ’ in describing the condition in malnourished Sudanese.

Atrophy

In starving people and those suffering from serious subnutrition as a result of debilitating disease, the skin may be thin and inelastic. Over the front of the legs it appears shiny and tightly stretched. This is due to a general failure in the nutrition of the cells that are normally concerned with maintaining the skin in health and replacing losses of epithelium from the surface. It cannot be ascribed to dietary deficiency of any single nutrient.

Pigmentary changes and colour

Nutritional failure can affect the colour of the skin in many different ways. The dirty brown pigmentation of the skin in chronic subnutrition has already been described, as well as the patchy hyperpigmentation and depigmentation often associated with kwashiorkor. In pellagra there is typically an erythema of exposed surfaces, whilst in anæmia the skin may be unduly pale. The hands of underfed children are often cyanosed, even in warm weather ; while in cold, damp climates they are often affected by chilblains.

Chilblains are common in Great Britain in winter-time, but are seldom seen in North America where the houses are centrally heated. Nutritional deficiencies have often been blamed for chilblains, on no good grounds. Calcium, nicotinic acid, vitamins D, E and K have all been recommended for their treatment. It is an axiom of Medicine that when numerous remedies are offered for a single disease, none is particularly effective.

Tropical ulcer

Chronic ulcers, affecting chiefly the lower limbs, occur in hot, damp climates among people whose tissues are vitiated by malnutrition. They used to be common in coolies employed on plantations; European prisoners of war working on the Burma-Siam railway were severely affected. Vincent's organisms and diphtheroid bacteria are commonly present in the lesions. They are certainly not attributable to lack of any one single nutrient. However, the presence of tropical ulcers in any community or labour force is a certain indication that the diet is unsatisfactory.

Skin ulcers of a different kind may occur in desert populations. The clinical features of 'desert sores' are very different from tropical ulcer; they afflict both the well-nourished and malnourished. Fair-skinned, red-headed people seem to be particularly susceptible. A poor diet will aggravate the lesions, but we have seen many British soldiers severely affected at a time when their diet appeared satisfactory in all respects.

Angular stomatitis

This is an affection of the skin at angles of the mouth, characterised by heaping-up of greyish-white sodden epithelium into ridges, giving the appearance of fissures radiating outwards from the mouth (Plate XIX, B). Secondary infection and staining by food may give the lesion a yellowish colour. It may extend across the mucocutaneous boundary and produce whitish patches on the mucous membrane lining the cheeks. In differential diagnosis it must be distinguished from other lesions in the same site, notably syphilitic rhagades, herpes labialis and lichen planus.

Angular stomatitis among pellagrins in the Southern States of the U.S.A. has been relieved by giving riboflavin by mouth. In Nigeria, where pellagra is seldom seen, the oral lesions also respond rapidly to large doses of riboflavin. Yet undoubtedly riboflavin deficiency is not always the main cause. Other patients have responded to pyridoxine. Angular stomatitis occurs in association with iron deficiency anæmia and other debilitating diseases.

Cheilosis.—This is the name given to a zone of red, denuded epithelium at the line of closure of the lips. It is frequently seen in pellagrins and is often associated with angular stomatitis. Both lesions may have a seasonal incidence and only appear during periods of drought and lack of fresh foods; but it is unlikely that lack of any one specific vitamin or other nutrient is usually the sole cause.

Oro-genital syndrome

In this condition, a lesion resembling angular stomatitis (which is always present and a feature of the syndrome) affects other mucocutaneous junctions. Soggy, whitish patches may appear at the outer angles of the eyes, within the ears, at the vulva or prepuce of the penis, and around the anus. Associated with these changes there is often corneal vascularisation (p. 233) and a scaly, greasy eczema at the angles of the nose, on the lips, chin and behind the ears. A dry, intensely itching, erythematous eczema, with a well-defined edge, may appear on the genitalia—the scrotum or mons veneris, over the perineum and down the inner sides of the thighs. If this eczema becomes secondarily infected, or invaded by maggots, the results may be terrible. The syndrome caused much distress among British prisoners of war in Japanese hands. There is general agreement that the syndrome responds well to natural preparations of the vitamin B complex such as yeast extract (*e.g.* Marmite), though not to any single synthetic vitamin.

Disorders of the hair and nails

In health the hair is sleek and glossy, often with a natural wave or curl. In malnourished or subnourished people the hair frequently becomes dull and lustreless; it is not easily brushed and tends to stand up straight (' staring hair '). At the same time the colour of the hair may change. In fair people it may turn to a dirty brown, while in black-haired people there may be loss of pigment, with a change of colour ranging from brown, rusty red to almost white. The depigmentation is sometimes seen in bands along the length of each individual hair, corresponding to previous alternating periods of poor and relatively satisfactory nutrition.

Contrary to some previous beliefs, white or grey hair in middle age or senescence has normally no nutritional significance. Nor is baldness a manifestation of nutritional failure. But a general sparseness of hair over the trunk may indicate a degree of sex-hormone insufficiency which may sometimes have a nutritional basis.

In chronic iron deficiency anæmia the finger-nails may be spoon-shaped. In other forms of malnutrition the nails may be brittle or thickened; they may be lined on the surface, either transversely or longitudinally; but these changes may also be seen in well-nourished people. Severe protein deficiency may result in opaque white bands in the nails, occurring symmetrically on both hands (Muehrcke, 1956).

Comment

Until more is known about the chemical pathology of the skin, hair and nails it will continue to be difficult to assess the significance of certain clinical changes in these structures which are sometimes seen on examination of underfed or malnourished people. There have been many varying descriptions given of these signs, and equally many interpretations offered for them. A helpful review of some of the large literature on the subject is provided by McCance and Barrett (1951).

DISORDERS OF THE EYE

Night blindness.—It has already been explained in Chapter 13 that vitamin A plays an essential part in the mechanism of vision in dim light. Night blindness is a frequent consequence of vitamin A deficiency. However, many factors besides vitamin A deficiency may contribute to complaints of night blindness. These include fatigue, emotional disturbances associated with acute danger and also chronic anxiety states. Moreover, there are organic causes such as retinitis pigmentosa. Night blindness arising from vitamin A deficiency always responds to suitable vitamin therapy and it is unwise to make the diagnosis before adequate therapeutic trials have been carried out.

In Southern India, where night blindness is very common—as also is vitamin A deficiency—the disorder is usually associated with a daily dietary intake of less than 600 i.u. of vitamin A activity. This level is far less than is usual in any European diet. In the past, night blindness has been a common complaint of the malingerer and is quickly learnt by others unless promptly dealt with. Unless the diet is known to be grossly deficient, or therapeutic trials have been carried out, it is best to assume that the cause of the blindness is not nutritional.

Xerophthalmia (Xerosis conjunctivæ) and Bitôt's spots

These conditions are frequently mainly attributable to vitamin A deficiency. The earliest sign is a peculiar smokiness of the scleral conjunctiva which also becomes very dry. The ducts of the tear glands become blocked by keratin. The scleral conjunctiva takes on a ' ground glass ' appearance and becomes thickened and easily thrown into folds by gentle pressure of a finger. Bitôt's spots are glistening white plaques formed of desquamated thickened conjunctival epithelium, usually triangular in shape and firmly adherent to the underlying conjunctiva. They are generally bilateral, on the temporal sides of the corneæ, and in coloured races are often surrounded by dense brown pigmentation. Plate XX, A, shows a characteristic spot. Pingueculæ should not be mistaken for Bitôt's spots ; these are yellowish accumulations of fatty material, generally on the nasal side of the scleræ, and placed close to the corneal margin. So far as is known they have no nutritional significance.

In young children, xerophthalmia is almost always attributable to recent vitamin A deficiency. In older children and in adults its interpretation is less simple. Pigmentation and a thickened conjunctiva may be evidence only of a *past* vitamin deficiency, since the conjunctiva of severely affected people returns to normal very slowly. Exposure to dust and glare may produce similar changes. The presence of some degree of xerophthalmia is thus not always certain evidence of continuing vitamin A deficiency in adults. It should, however, always call attention to the diet. Xerophthalmia by itself may not cause any disability, unless associated with night blindness. The condition, however, always merits serious consideration as dryness of the conjunctivæ always precedes the development of keratomalacia (Chapter 35). In the past Bitôt's spots have been usually associated with vitamin A deficiency and they are frequently present in children whose diet has been grossly lacking in this vitamin. However there is convincing evidence (Rodger, 1960; Darby *et al.*, 1960) that the condition can be present when there are no other signs of lack of vitamin A and the diet provides ample quantities of the vitamin or its precursor, beta-carotene.

Pigmentation of the conjunctiva is frequently associated with xerophthalmia. Pigment may be deposited (1) round the cornea (pigmented ring), (2) in the lower eyelid (pigmented gutter) and (3) over the sclera equatorially in the area commonly occupied by Bitôt's spots. The significance of this pigment formation is uncertain.

Corneal vascularisation

The essential lesion in this condition is an invasion of the normally avascular *cornea* by capillary blood vessels. These vessels cannot be seen with the naked eye, nor with an ordinary hand lens. A slit-lamp microscope in the hands of an experienced observer is needed for positive identification. Small greyish-white opacities may also be seen on the surface of the cornea. The patient usually complains of a burning sensation in the eyes, misty vision, lachrymation and photophobia—the latter symptom may make slit-lamp examination difficult. Associated with the condition there is often injection of the *conjunctiva* with dilated blood vessels which are easily visible on simple inspection, without the use of a slit-lamp. However, the presence of an injected conjunctiva should not allow the assumption that a vascular cornea is also present; it may arise independently as a result of a great variety of causes.

Sydenstricker and his colleagues (1940) first described corneal vascularisation in pellagrins; they showed that in such patients it could be relieved by giving riboflavin by mouth. However, it is now clear that other factors besides lack of riboflavin can produce a keratitis identical in appearance with that described by Sydenstricker. The occasional case encountered in Great Britain seldom responds to the vitamin. Indeed there are many other causes of superficial keratitis, some quite unconnected with malnutrition.

In the oro-genital syndrome, lachrymation, photophobia and conjunctival injection are commonly present. If a slit-lamp is not available for examining such cases, the presence of nutritional keratitis may be inferred, and riboflavin therapy tried. Some natural source of the vitamin B complex, such as yeast extract or rice polishings, has proved of value in such cases.

Trachoma is a virus infection of the eye to be distinguished from corneal vascularisation and keratomalacia (Chapter 35). It usually affects first the inner surface of the upper lid, extending later to the cornea.

Plate XIII A. Prisoners in a concentration camp. (From Helweg-Larsen *et al.*, 1952.)

Plate XIII B. Children suffer particularly under famine. This photo was taken in Kasai in the Congo in 1962. (Photo Atlantis.)

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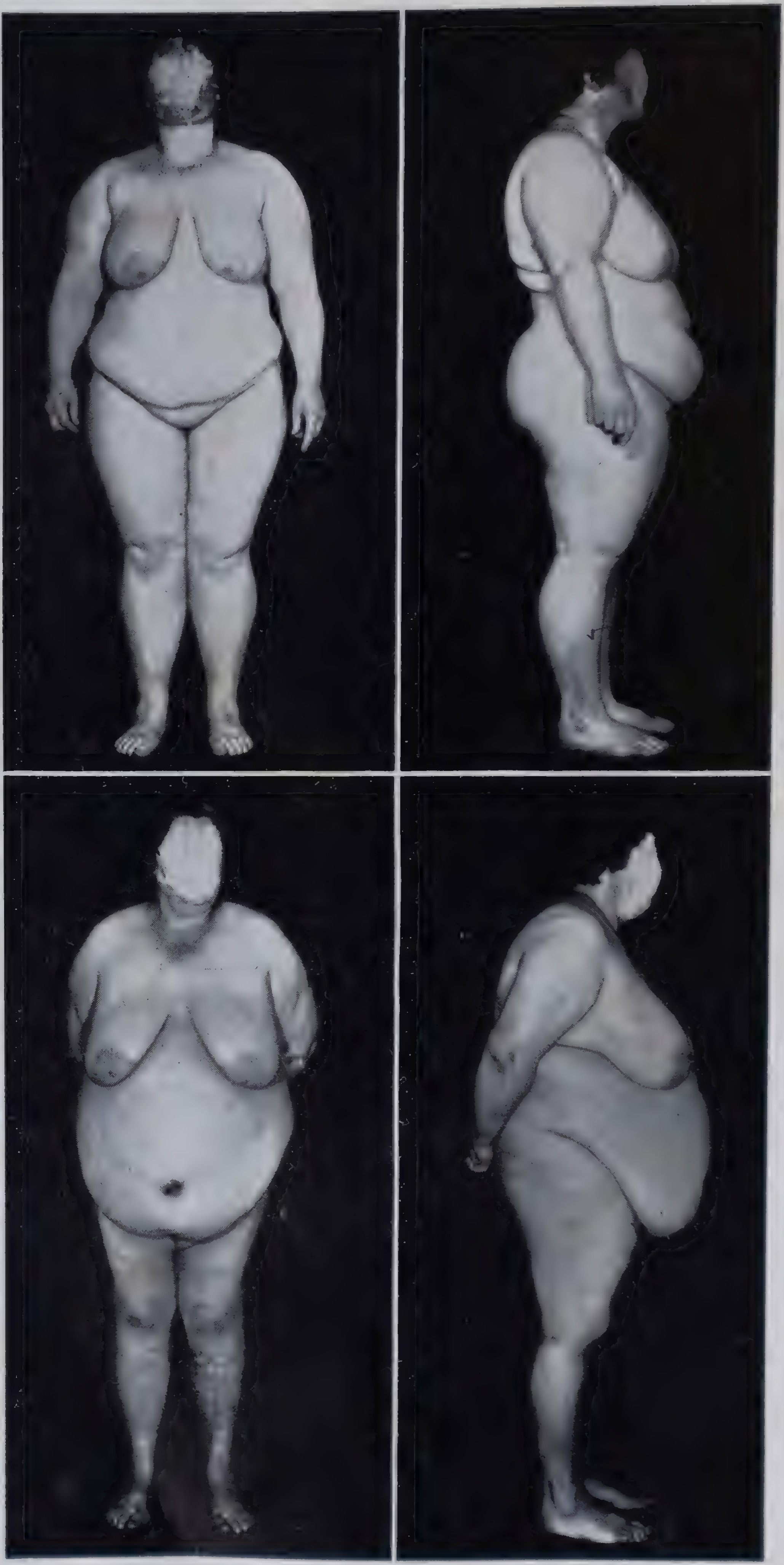
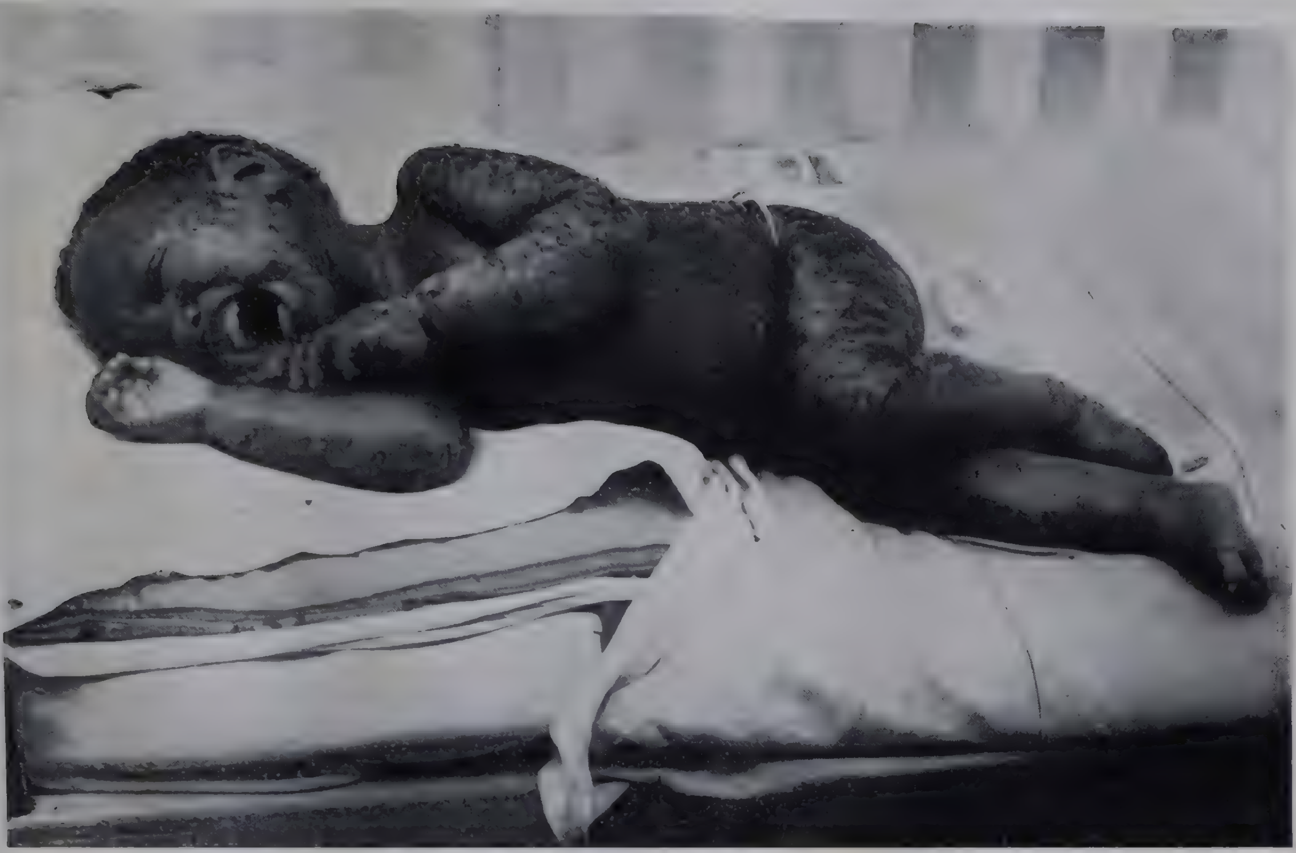


Plate XIV. Two obese women, weighing 106 kg. and 160 kg. respectively.



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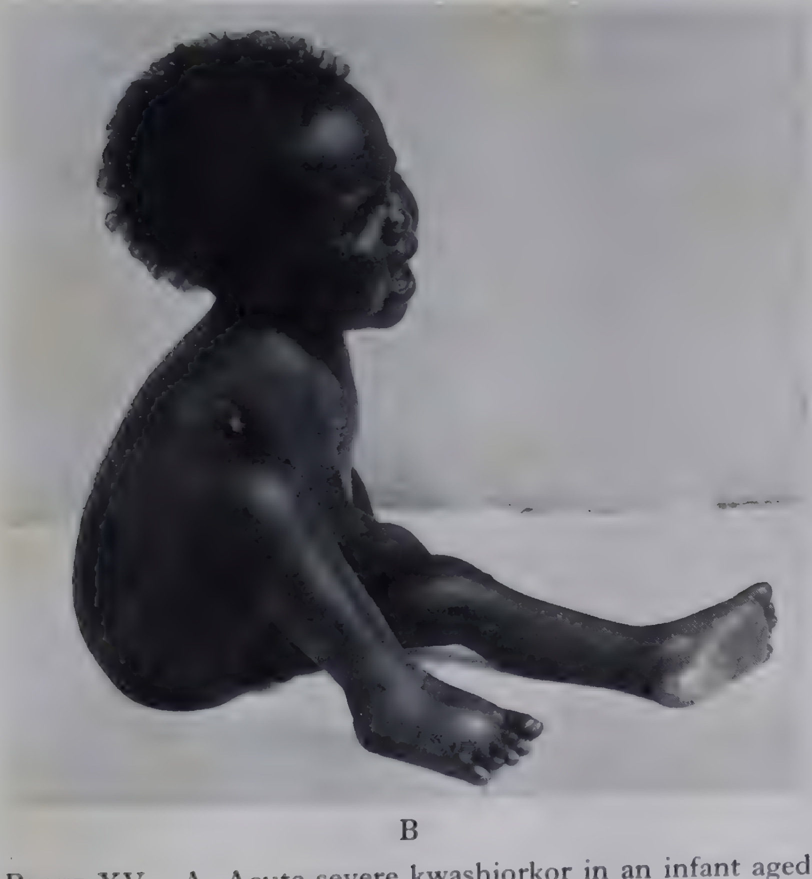


B

PLATE XV. A, Acute severe kwashiorkor in an infant aged 6 months. The disease was precipitated by an attack of measles and the rash is visible all over the skin. No emaciation, and œdema is not marked. The child died suddenly next day. A patient of Dr Meredith, Tanganyika. B, Early kwashiorkor. Note œdema and facial expression. A patient of Dr M. Clark, Kenya.

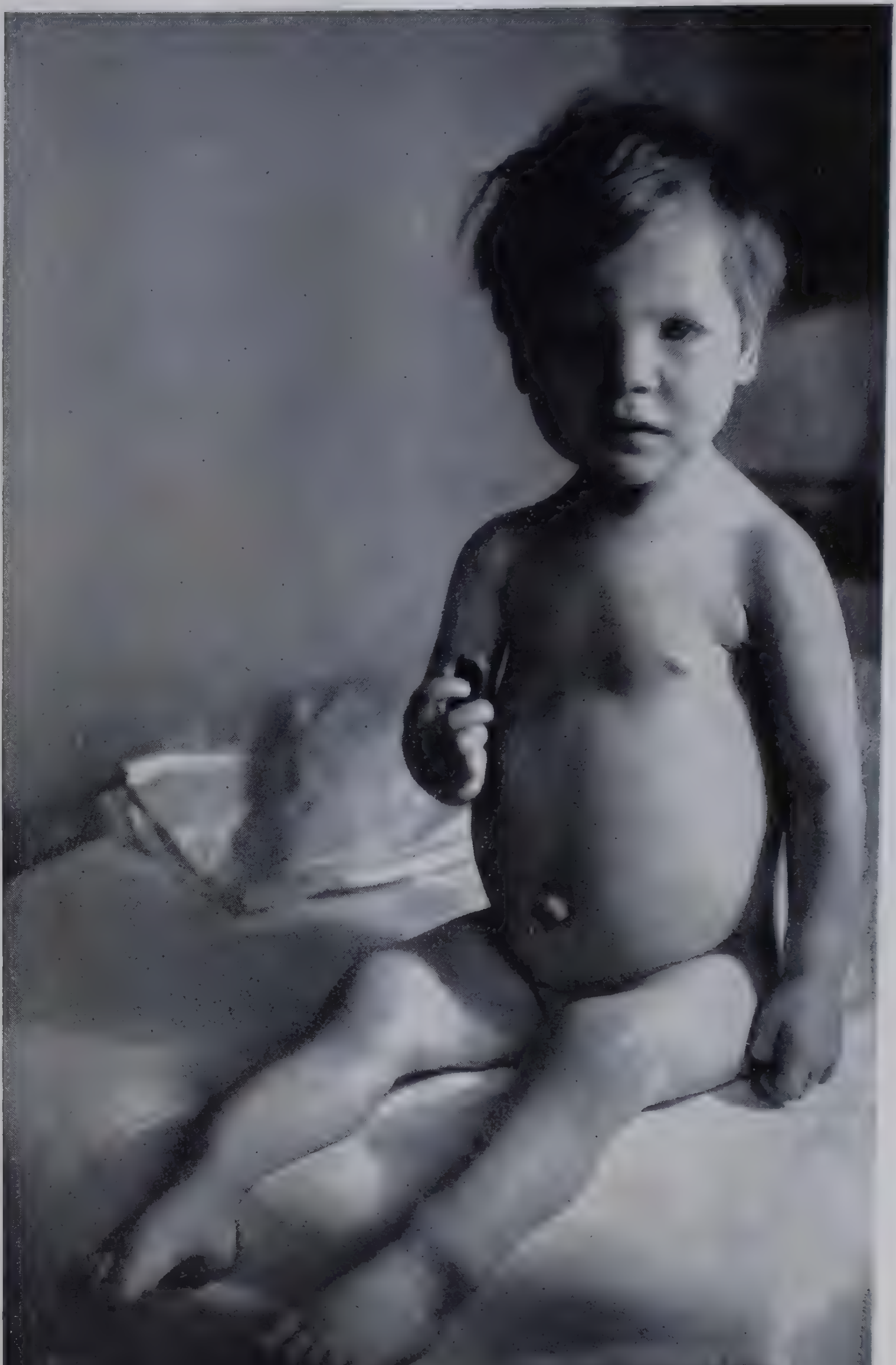
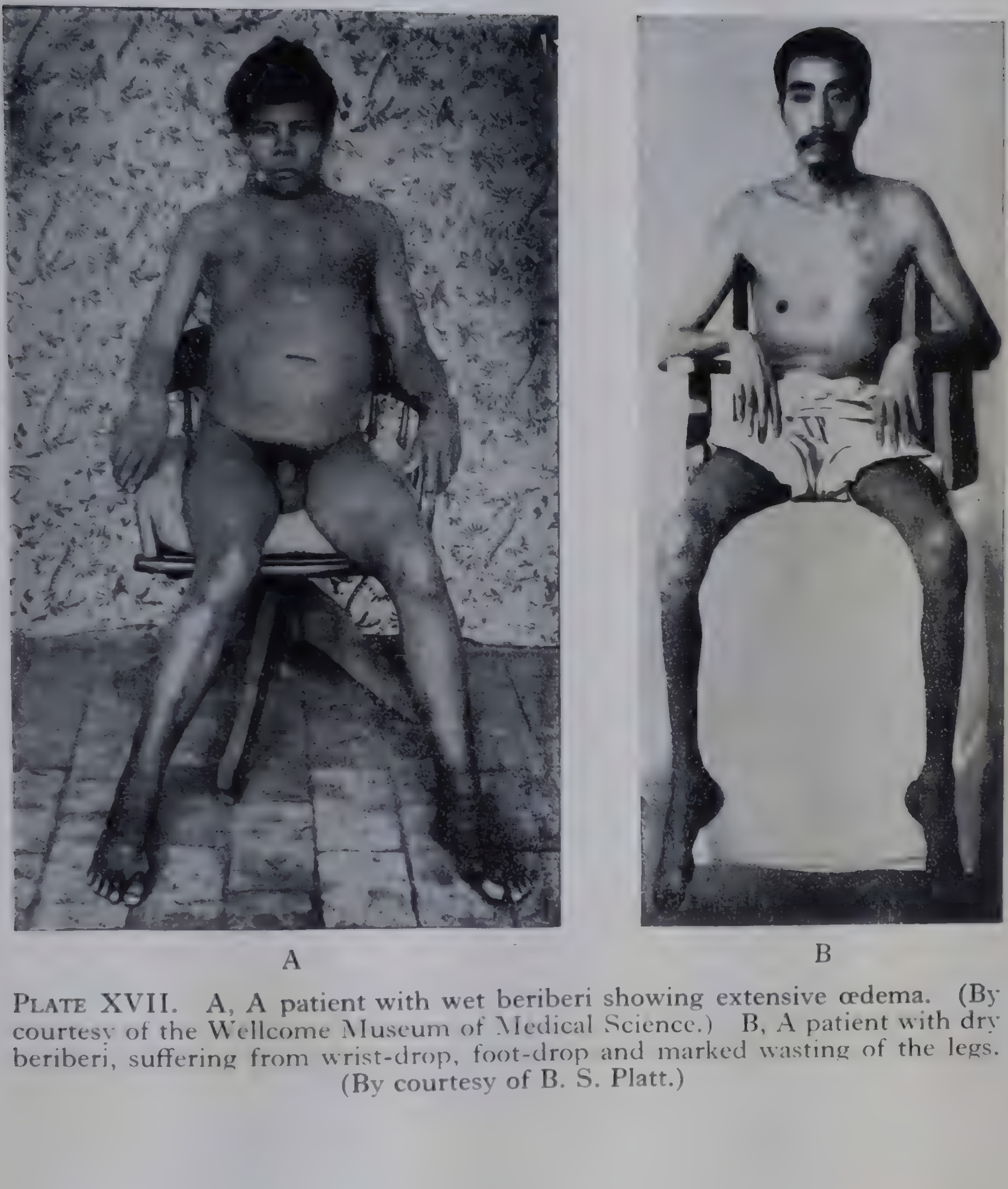
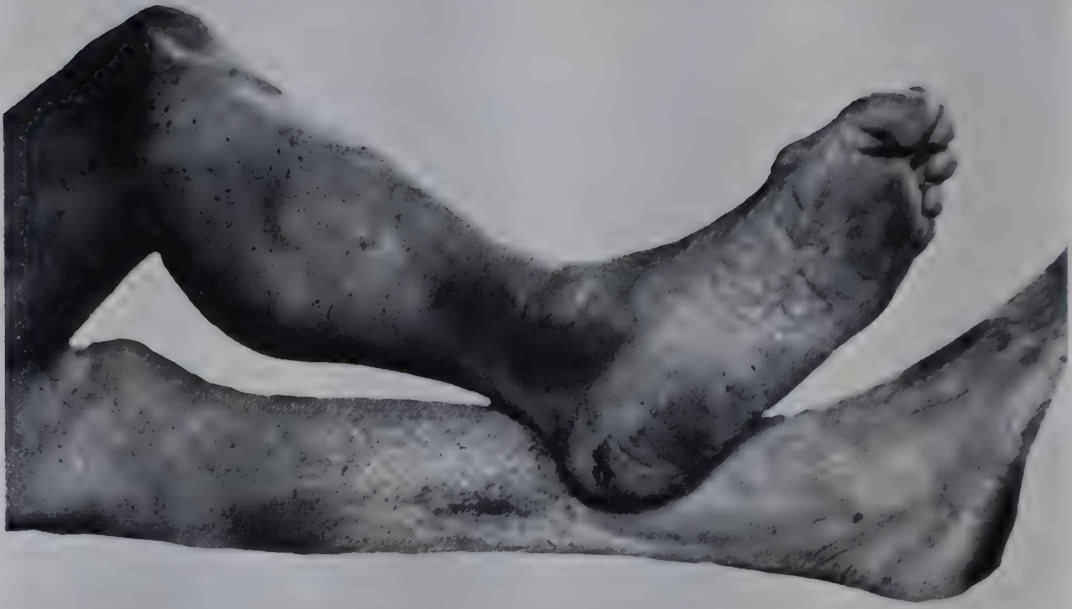


PLATE XVI. Rickets. Note the anterior-posterior bowing of the legs with epiphyseal enlargement at both ankle and wrist. The general nutrition is good. (By courtesy of Stanley Graham.)



A B

Plate XVII. A, A patient with wet beriberi showing extensive œdema. (By courtesy of the Wellcome Museum of Medical Science.) B, A patient with dry beriberi, suffering from wrist-drop, foot-drop and marked wasting of the legs. (By courtesy of B. S. Platt.)



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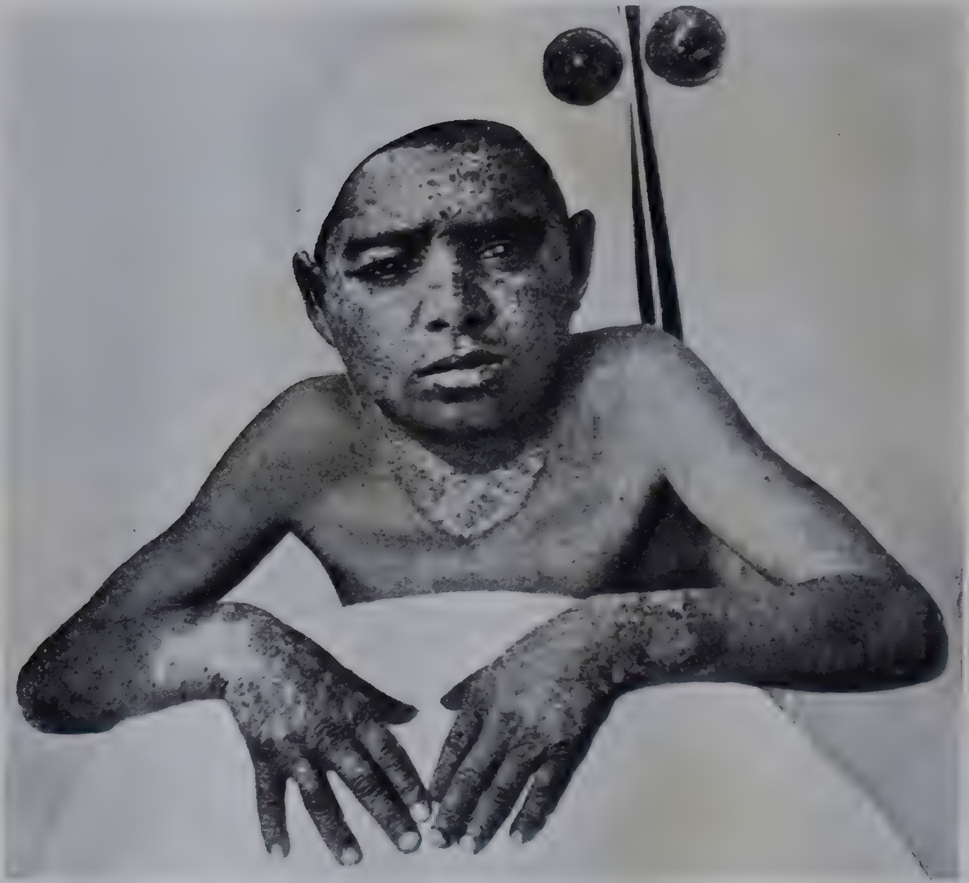
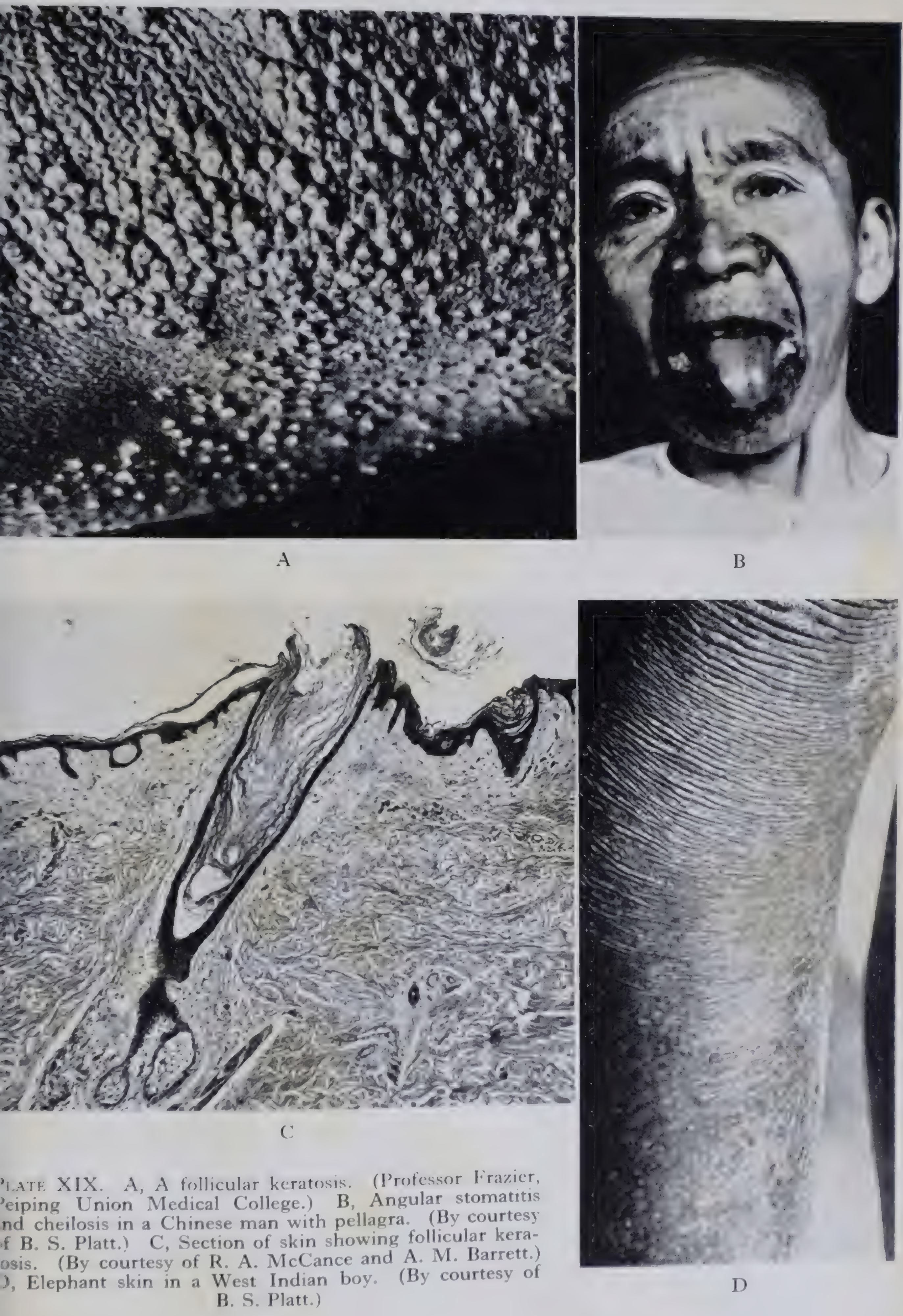
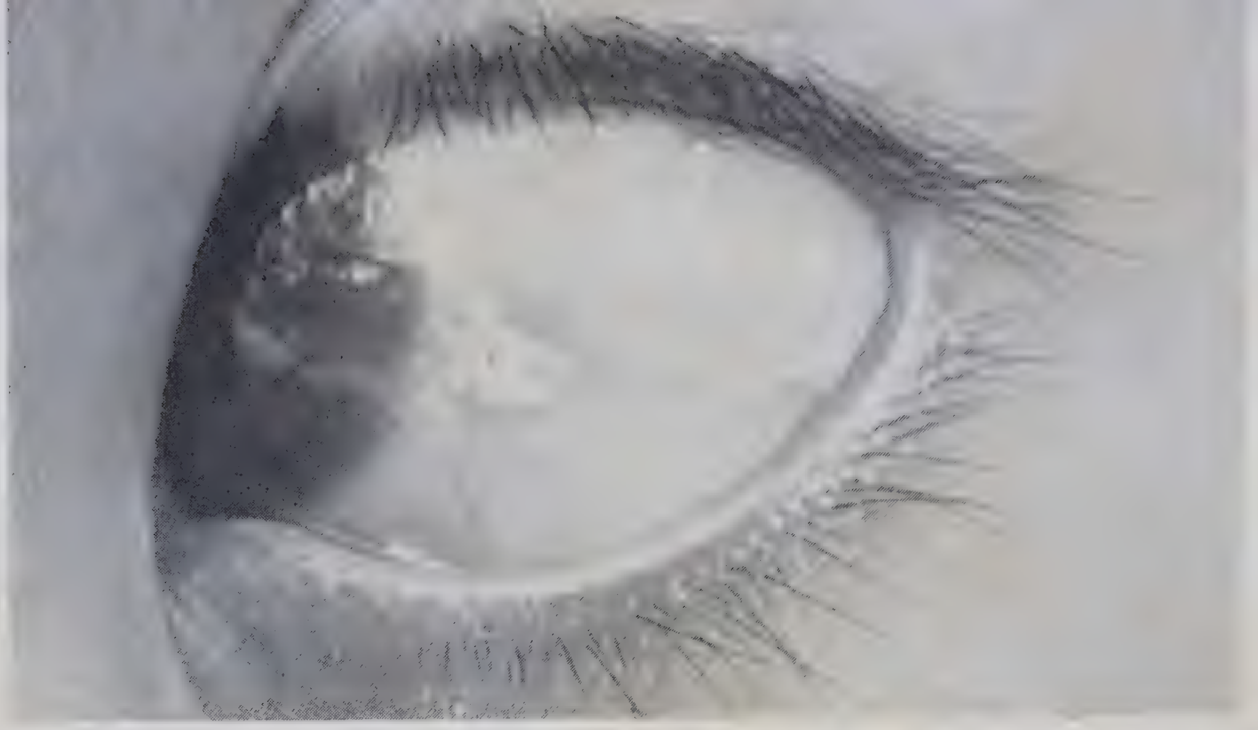


B

PLATE XVIII. A, Legs of a patient with scurvy showing perifollicular hæmorrhages about the left knee, a large bruise behind the left ankle and petechial hæmorrhages on the right leg. (A case in the Royal Infirmary, Edinburgh.) B, A typical case of pellagra in an Egyptian. The dermatitis is confined to the skin surfaces exposed to sunlight. (C. H. Lavinder and J. W. Babcock's case. From STITT, E. R. *Tropical Diseases*. McGraw-Hill Book Company Inc.)



LATE XIX. A, A follicular keratosis. (Professor Frazier, eiping Union Medical College.) B, Angular stomatitis nd cheilosis in a Chinese man with pellagra. (By courtesy f B. S. Platt.) C, Section of skin showing follicular keraosis. (By courtesy of R. A. McCance and A. M. Barrett.)), Elephant skin in a West Indian boy. (By courtesy of B. S. Platt.)



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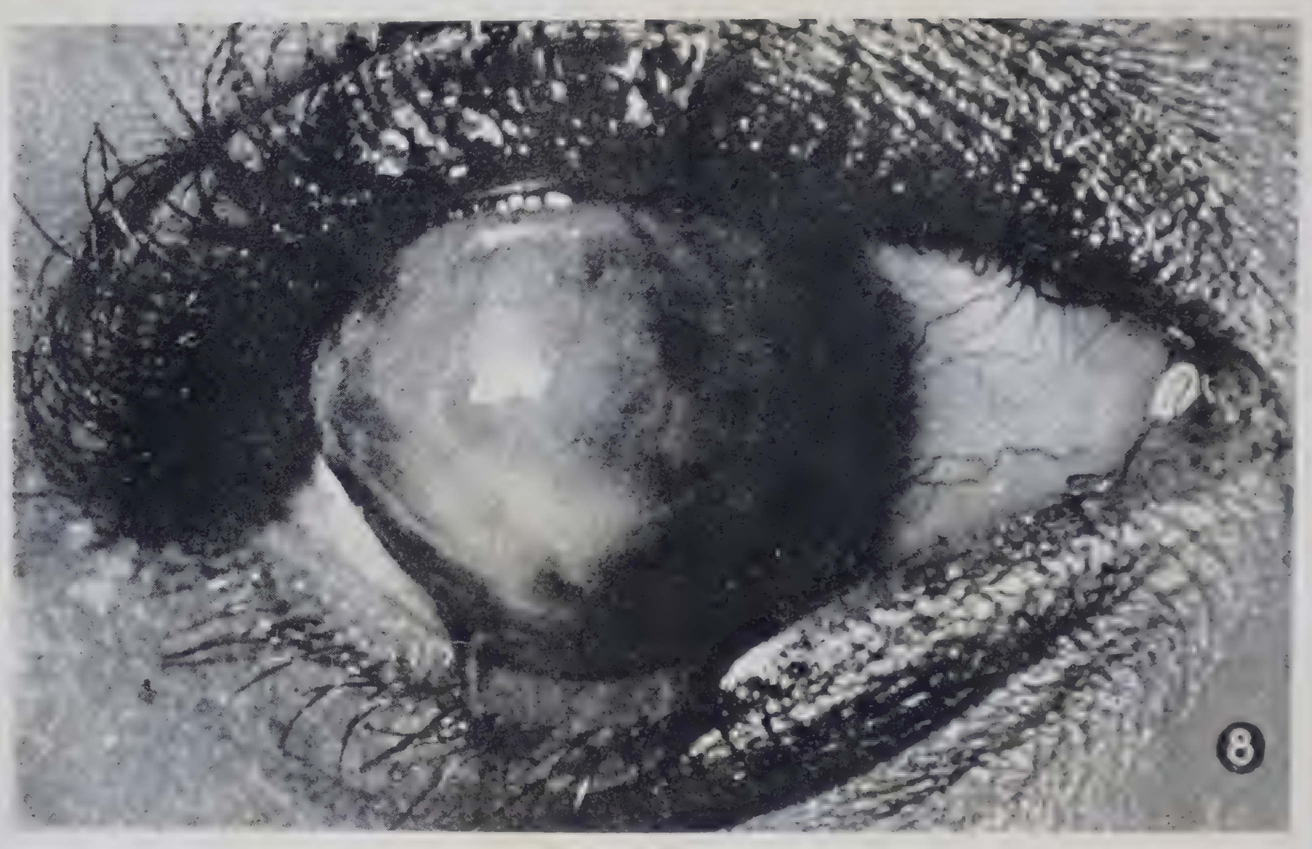

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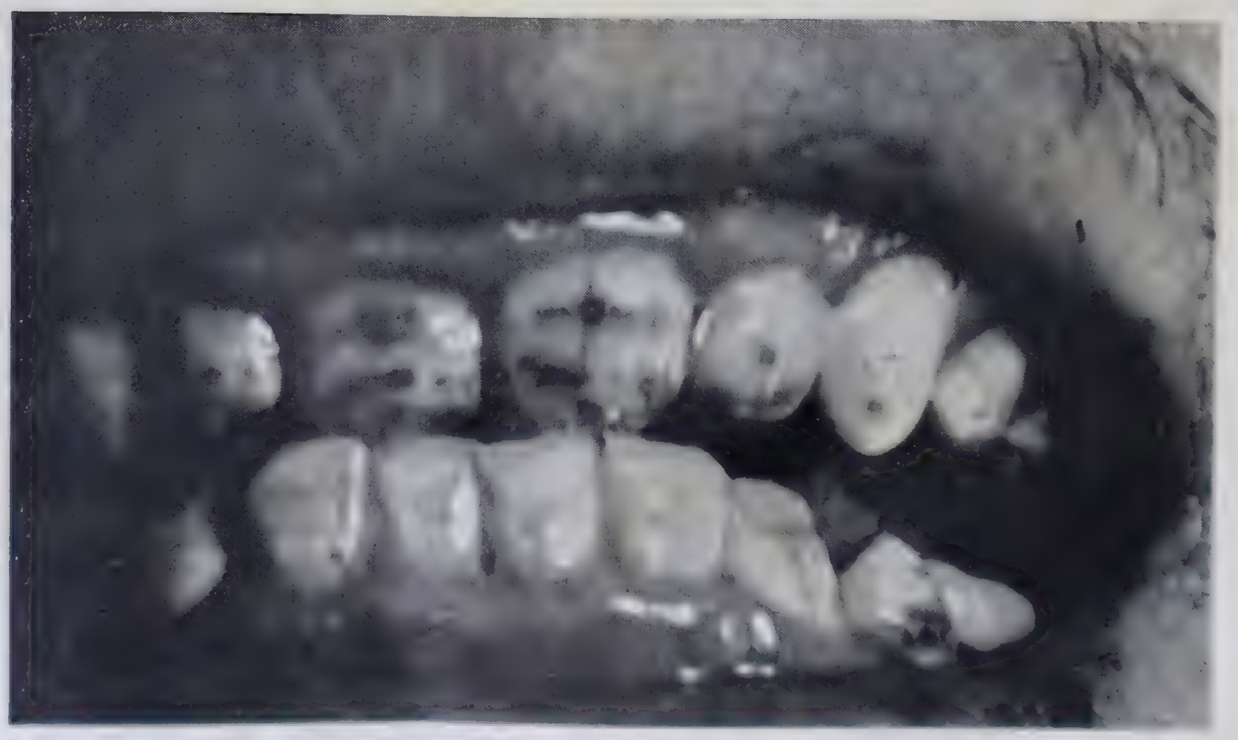

C

Although many sufferers from trachoma are malnourished, as yet there is no certain evidence that nutritional factors play any part in its causation.

Nutritional amblyopia is a major nutritional disorder of the eyes ; it is discussed in Chapter 33.

Disorders of the Mouth

Angular stomatitis and cheilosis have already been described earlier in this chapter.

Nutritional glossitis

Deficiencies of nicotinic acid, riboflavin, vitamin B_{12}, folic acid and iron may all give rise to glossitis. It is a feature of pellagra, sprue and nutritional anæmias. The tongue seems to be particularly susceptible to metabolic disorders of all kinds. When a sudden and severe restriction in the supply of one or other of the above nutrients occurs, acute glossitis develops. If the deficiency is partial and extends over months or years, chronic atrophic glossitis is more often seen. In acute glossitis the tongue is swollen, sometimes to such an extent that it is continually pressed against the lower jaw and well-marked dental impressions are visible. The papillæ are usually very prominent. The colour of the tongue is characteristically red, but in some cases it may have a purplish hue. The mucous membrane sometimes desquamates in patches leaving areas of red raw surface. Deep irregular fissuring is common and shallow ulcers may occur, especially on the sides or tip. The tongue may be extremely painful, so much so that fear of pain may prevent the patient from eating. In chronic atrophic glossitis the tongue is small, with an atrophic mucous membrane and small or absent papillæ so that its surface appears smooth, moist and abnormally clean. Fine fissuring may be present. It is not painful.

There are those who claim to be able to distinguish the appearance of the tongue in nicotinic acid deficiency from that of vitamin B_{12}, folic acid or riboflavin deficiency ; the last is said to be magenta in colour. But the distinction is not important as in nearly all cases there has been a multiple dietary deficiency of vitamins.

Nutritional glossitis is commonly found when supplies of milk, fresh vegetables and other protective foods are not available. It is often seen in association with angular stomatitis and both may have a seasonal incidence associated with temporary dietary shortages. The condition often quickly disappears following minor improvements in the diet. Skimmed milk and dried yeast are frequently curative. In pellagra the tongue responds dramatically to nicotinic acid (Chapter 34), as is the case

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PLATE XX. A, Bitôt spot. Triangular spot with the base reaching the corneal margin and the surface covered with white adherent foam. Tamil boy aged 10. (By courtesy of Dr P. Fasal.) B, Keratomalacia in a Bantu child. (BLUMENTHAL, 1950.) C, Fluorosis in a Sudanese man. (By courtesy of Professor D. A. Smith.)

with the acute glossitis of pernicious anæmia treated with vitamin B_{12} or the glossitis of the sprue syndrome treated with folic acid.

Jeghers (1942) has provided a useful review of the literature on nutritional and other disorders of the tongue.

Parotid gland enlargement

Swelling of the parotid glands is found among children in some parts of Africa and Asia. Raoult and his associates (1957) have made an extensive study of the condition in French West Africa and produce convincing evidence that the swellings are nutritional in origin, and lack of adequate protein a probable cause. The swellings may increase slowly and persist for years ; on the other hand, with an improvement in the diet they may disappear quickly. The condition may readily be confused with mumps.

Histological examination of the swollen gland shows hypertrophy of the acini. In the final state, fibrosis develops with cystic dilatation of the ducts—a parotid cirrhosis.

Disorders of the teeth and gums are discussed in Chapter 54. Nutritional factors in relation to disorders of the remainder of the gastrointestinal tract are discussed in Chapter 38.

PART IV

NUTRITIONAL ASPECTS AND DIETETIC TREATMENT OF GENERAL DISEASES

CHAPTER 38

DISEASES OF THE DIGESTIVE SYSTEM

EVERY patient suffering from a disease or disorder of the digestive system must be carefully questioned about his dietary and social habits. This includes information about the number and time of the meals taken daily, whether they are taken regularly, if they are hurried, and if the food is adequately chewed. A description must be obtained of the various foods eaten and of their effects in alleviating or producing the symptoms. Particular enquiry must be made into the taking of excessive quantities of alcohol, especially on an empty stomach, strong tea or coffee at too frequent intervals, or indigestible articles of food and condiments, A careful history should be obtained to find out about the patient's smoking habits and whether he or she is living in a state of tension consequent on anxiety induced by abnormal social relations at home or at work. We have repeatedly seen dyspepsia developing when a love affair is not proceeding on a satisfactory course, when an employee is being bullied by an employer, or when some financial misfortune is causing undue worry. This conception is of great importance because the restoration of the physiological working of the alimentary tract by the correction of faulty habits and anxiety states is an essential part of the prevention and treatment of both organic and functional disease, and is as important as the diet or drugs prescribed.

In diseases of the gastrointestinal tract, it is common sense to see if the teeth are mechanically efficient. The reduction of foodstuffs to a soft pulp by mastication is a prerequisite to good digestion. It is essential, therefore, to find out whether the patient has sufficient teeth in his mouth, and whether those in the lower and upper jaws are in apposition. If dentures are used they must be comfortable, otherwise they may be put in for æsthetic purposes at social functions, but removed at meal times.

When prescribing a diet for a patient suffering from any disease of the alimentary or indeed any other system, it is essential to bear in mind the following points.

1. Be sure that the diet is well balanced and satisfactory in relation to calories, carbohydrates, protein and fat, with adequate minerals and vitamins.

2. Remember, if attention is directed solely to the dietetic treatment

of a particular symptom—*e.g.* diarrhœa, gastric pain—the general nutrition of the patient may suffer.

3. Consider the patient's economic status and occupation and see that the dietary regime ordered is suitable in each individual case. Obviously different schemes will be required for an office worker, a miner and a night watchman.

4. Give due consideration to the individual's likes and dislikes for different articles of food. Never prohibit an article from a diet unless there is a clear history of a personal idiosyncrasy to it, or unless there is adequate clinical or experimental evidence for its exclusion.

5. Remember that the dietetic requirements of acute and chronic disease may be very different. Thus, in intense diarrhœa, excessive vomiting, or infections which are severe in degree but short in duration, *e.g.* acute food poisoning and lobar pneumonia, the essential need is for fluids, glucose and salt to prevent or correct dehydration, ketosis, and loss of electrolytes. In long-continued diseases, such as pulmonary tuberculosis or ulcerative colitis, the diet must be adequate both in quantity and quality.

DISEASES OF THE MOUTH

Examination of the mouth may show lesions due to local causes, lesions indicative of general disease, or lesions which are primarily nutritional in origin. These include angular stomatitis, cancrum oris, nutritional parotitis and nutritional glossitis (Chapter 37). Glossitis is often a presenting feature in pellagra, the sprue syndrome, pernicious anæmia and iron deficiency anæmia of long standing.

The tongue.—Doctors have examined the tongues of their patients since the earliest times. Stress has been laid on whether the tongue is (1) clean or dirty, (2) dry or moist, (3) smooth or rough, (4) ulcerated or inflamed. A clean red tongue, which is inflamed and painful (acute glossitis) suggests an acute primary deficiency of some member of the vitamin B complex. A scrupulously clean, pale and smooth tongue (chronic atrophic glossitis) suggests pernicious anæmia or a long-standing iron deficiency anæmia with achlorhydria. Local ulceration of the tongue is usually due to mechanical irritation by irregular teeth or badly fitting dentures, but it may be an indication of a grave disorder such as malignant disease or, more rarely, syphilis or tuberculosis.

Treatment of the nutritional disorders of the tongue consists in prescribing a well-balanced diet, supplemented by iron or the appropriate vitamin.

The teeth, gums and mouth.—The part played by nutritional factors in the development of the teeth and in reducing their susceptibility to caries is discussed in Chapter 54. The importance of mastication of food in the prevention of dyspepsia has already been mentioned. The most common local inflammation of the gums is pyorrhœa alveolaris (periodontal disease). Root abscess is an even more important source of sepsis. The importance or otherwise of such focal sepsis in the causation of diseases such as gastritis, peptic ulcer and ulcerative colitis has long exercised the minds of doctors. At one time sepsis in the mouth or in the nasopharynx was considered an important cause of these diseases. It was postulated that swallowing of purulent infected material may irritate or infect the gastric mucosa, and that toxins absorbed into the general circulation may adversely affect the digestive tract. The possible deleterious effects of swallowing septic material in the production of chronic gastritis deserves consideration. There is no satisfactory evidence that any disease of the digestive system is caused by toxins or bacteria carried in the blood stream from septic foci in the mouth or nasopharynx. Previous opinions to the contrary were based mainly on the belief that focal sepsis was more common in such patients than in healthy controls. This has been shown to be incorrect. Nevertheless we do not believe that definite foci of infection should be neglected since they may be a potential source of toxæmia or bacteræmia. In fact we recommend on general principles that infections of the teeth and gums should be treated. Whenever possible this should be by conservative methods.

Inflammatory and hæmorrhagic lesions in the mouth and gums can result from a wide variety of causes, *e.g.* infections with Vincent's organisms, hæmolytic streptococci, *Candida albicans* (thrush), from poisoning with heavy metals (mercury, gold, arsenic, etc.), from some drugs (iodides, salicylates, phenytoin, etc.) or from certain serious blood diseases (acute leukæmia, agranulocytosis, aplastic anæmia). Recurrent aphthous ulceration of the mouth is common, but the cause is not known, although it is certainly not due to a nutritional deficiency. Any inflammatory condition of the mouth may contribute to a nutritional disorder, for the associated pain and difficulty in swallowing may restrict the intake of food.

Treatment.—The treatment of angular stomatitis, glossitis and other primary nutritional disorders of the mouth has already been described in Chapter 37. There is no satisfactory evidence that any of the other lesions of the mouth mentioned above are improved by dietary therapy. Local and general treatment on the appropriate lines, the removal of the causal condition, the use of antibiotics when necessary, and attention to oral hygiene should be instituted. If the lesions are causing pain on chewing or swallowing, a semi-fluid or fluid diet (Diet No. 2) should be advised temporarily until the condition is brought under control. The use of a straw or a glass tube to take fluids directly to the back of the mouth may occasionally be helpful.

THE SALIVARY GLANDS

Ptyalism and xerostomia.—Excessive secretion of saliva is called ptyalism, while a diminished secretion leads to conditions of dry mouth called xerostomia. There are many causes for ptyalism and xerostomia but nutritional deficiency is not one of them. Treatment consists of the removal of the cause and the administration of drugs for the relief of symptoms.

Parotitis.—The enlargement of the parotid glands common in Asia and Africa and associated with inadequate intakes of protein has already been described (p. 482).

Inflammation of the parotid glands may be due to the virus of mumps (specific parotitis) or to bacterial infection of the glands which tends to develop during severe febrile illnesses and after major surgical operations if adequate attention is not given to careful oral hygiene and to the prevention of dehydration and toxæmia. Septic parotitis is much more rarely encountered to-day than formerly. Its treatment consists of the parenteral administration of a suitable antibiotic and surgical drainage if abscess formation has occurred.

Acute parotitis from any cause is often so severe as to make swallowing painful and difficult. A fluid diet, based on Diet No. 2, should be given until the inflammation subsides.

DISEASES OF THE ŒSOPHAGUS

Diseases of the œsophagus are much less common than diseases of the stomach or intestines. Difficulty in swallowing (dysphagia) is the main clinical feature. Dysphagia may be due to functional causes, to neurological disorders of the peripheral nerves or brain, or to extrinsic compression or intrinsic disease of the œsophagus. The œsophagus may be affected by spasm, inflammation, trauma or malignant disease. The three last conditions frequently terminate in stricture.

Paterson-Kelly Syndrome.—The only disease in which nutritional deficiency is undoubtedly of ætiological importance is the Paterson-Kelly (Plummer-Vinson) syndrome. In this the features are iron deficiency anæmia, glossitis, dysphagia and achlorhydria. Degenerative changes occur at the junction of the pharynx and the œsophagus, and these may lead eventually to deformity in the form of a mucosal web in the upper œsophagus. The disease is usually found in middle-aged women and the principal complaint is difficulty in swallowing. It only arises after severe iron deficiency has been present for several years. Lack of iron appears to be the primary cause of the syndrome. The condition was common 30 years ago when iron deficiency anæmia was much more frequent and severe than it is at the present time, but the improved social and economic conditions and the earlier diagnosis and better treatment of iron deficiency have made it rare now in Great Britain. This is indeed fortunate because the syndrome predisposes to carcinoma. Treatment consists in giving a well-balanced diet which should be fluid or semi-fluid (Diet No. 2), depending on the degree of dysphagia present, together with adequate amounts of medicinal iron. If the response to iron by mouth is poor, iron must be given parenterally. Occasionally surgical treatment may be required to correct the anatomical deformity.

Achalasia (Cardiospasm).—It has been suggested that the difficulty in swallowing which is the characteristic feature of this disorder is probably not due to spasm of the œsophagus, but to a failure in muscular relaxation preceding the advancing peristaltic wave. Hence, the name achalasia. This failure may be the result of degenerative changes in Auerbach's plexus in the wall of the œsophagus. This has been demonstrated occasionally in cases of dysphagia and achalasia occurring in pellagra and other states of vitamin B deficiency.

The dysphagia, which is at first intermittent, may become more and more persistent. In time the œsophagus becomes secondarily dilated and later, consequent on stagnation of food and infection from the nasopharynx, an œsophagitis frequently results with the production of considerable substernal pain. The diagnosis should be confirmed by radiological examination and œsophagoscopy, as it is essential to exclude an obstructive lesion due to malignant disease.

Achalasia is treated by drugs (sedative and antispasmodic) and by a bland diet (Diet No. 4), low in roughage. Should this not relieve the dysphagia, dilatation by the Negus hydrostatic bag or Stark manual dilator should be carried out. Should dilatation fail, surgical treatment (Heller's operation) will be required.

Stricture.—Difficulty in swallowing, first of solid foods and later of semi-solids and liquids, is the presenting feature of stricture. Relief must be obtained by surgery or radiotherapy or by dilatation and passing a Souttar's tube. Before the excision of a stricture it may be advisable to feed an emaciated patient for several days either by a nasogastric tube or a tube inserted directly into the stomach or jejunum at operation (Chapter 48). In inoperable cases life may sometimes be prolonged by feeding through such a tube in the stomach or jejunum ; this procedure should rarely be undertaken in a patient dying of a malignant stricture.

Hiatus hernia and reflux œsophagitis.—In recent years œsophageal hiatus hernia and its sequel, reflux œsophagitis, have been recognised as common causes of dyspepsia and dysphagia. The diaphragm has several openings through which herniation of abdominal viscera into the thorax can occur. Of these openings the most important is the œsophageal hiatus through which the œsophagus passes and to which it is loosely attached. In middle-aged and elderly people particularly, this attachment weakens so that herniation of the œsophagus and stomach readily results. Many of these hernias are symptomless and are discovered accidentally by the radiologist, if he makes a practice of examining all his patients not only standing up but also lying down. Hiatus hernia usually only gives rise to symptoms in so far as the sphincteric action at the cardia is lost and free regurgitation of acid peptic juice occurs. This produces the condition of *reflux œsophagitis*. The cardinal symptom of reflux œsophagitis is heartburn, which is felt substernally and may be accompanied by regurgitation of fluid into the mouth. This heartburn may occur after meals but is also and typically associated with a change of posture, *e.g.* bending down at housework, or lifting or straining, which produces a rise of intra-abdominal pressure. It may occur on lying down at night and may waken the patient, who obtains relief by sitting up. There is no other pain produced in the alimentary tract which is so closely linked to change of posture. The patient may also complain of more severe pain or the sensation of food sticking which may amount to dysphagia. Bleeding not infrequently occurs in patients with hiatus hernia, and may be suspected as the cause of an obscure iron deficiency anæmia.

The majority of patients with reflux œsophagitis are elderly and can usually be maintained free from symptoms by medical treatment. The patient should take a bland diet, and if there is considerable obesity a serious attempt should be made to reduce weight. Patients particularly distressed with pain at night should be taught to sleep in a semi-upright position, with the head of the bed raised on blocks, to diminish regurgitation of gastric juice. If the pain is at all severe, the regime should be of the ulcer type with hourly antacids continued until the œsophagitis subsides. Anæmia which is due to bleeding should be treated with oral iron, or in severe cases with blood transfusion. Pain which persists despite efficient medical treatment may require surgical treatment for its relief. Such pain is likely to be associated with ulceration and some degree of stricture formation.

Peptic ulceration.—The œsophagus is also subject, like the stomach and duodenum, to peptic ulceration if exposed to acid gastric juice. This frequently happens if a hernia through the hiatus in the diaphragm impairs control of the sphincter and the acid contents of the stomach are allowed to reflux into the œsophagus. Peptic ulceration of the œsophagus is treated, as in the stomach and duodenum, by rest, posture, alkalis and diet.

THE STOMACH

Physiology.—The primary function of the stomach is to act as a storehouse so that food need only be ingested 3 or 4 times a day. In this way the inconvenience of eating many small meals is avoided. The lack of this storehouse, as after complete gastrectomy, is always a considerable handicap to the patient, and is inevitably followed by loss of weight. While the cardiac end and body of the stomach, which are sluggishly motile, are chiefly concerned in this reservoir function, the mixing and churning movements are carried out in the pyloric antrum. These variations in physiological role are related to differences in anatomical structure.

Dyspepsia

Definition.—Dyspepsia is a word of Greek derivation, meaning indigestion or difficulty in digestion. Any symptom associated with the taking of food is called dyspepsia (*e.g.* nausea, heartburn, epigastric pain, discomfort or distension). Dyspepsia may be present when there is no structural change in any part of the alimentary canal, in which case it is described as ' functional.' On the other hand dyspepsia may be a symptom of œsophagitis, gastritis, peptic ulcer, gastric cancer, or any organic disorder of the alimentary canal. It may also be caused reflexly by disease or disorder of structures outside the alimentary tract, *e.g.* the gall-bladder, pancreas, etc. Dyspepsia may, in addition, be a symptom of a general disease, *e.g.* pulmonary tuberculosis, chronic nephritis, cardiac failure or cirrhosis of the liver.

Dyspepsia and acid secretion.—There is a great variation both in the quantity and concentration of acid which may be secreted by the gastric glands. It was once thought that dyspepsia frequently arose as a result of too little or too much acid secretion. However, good digestion may be associated with the whole range of gastric acidity. For instance, patients with pernicious anæmia always have complete absence of acid secretion (*achylia gastrica*) and yet seldom suffer from dyspepsia when the anæmia has been corrected by treatment with vitamin B_{12} (cyanocobalamin). It is very doubtful if lack of acid alone is ever responsible for digestive disturbances. Hence the term ' achlorhydric dyspepsia ' is not warranted.

When dyspepsia occurs with achlorhydria, it is probably due to coincidental conditions such as chronic gastritis, cancer of the stomach or disease of the gall-bladder, or to emotional states. Likewise, high rates of acid secretion (hyperchlorhydria) may be found in people who have never suffered from dyspepsia. Hyperchlorhydria is frequently found in patients with duodenal ulcer, yet such patients may continue to secrete excessive amounts of acid, not only when they are having symptoms, but during long intervals when they are symptom-free. Hydrochloric acid may be partially responsible for the pain and dyspepsia of the acute stage of peptic ulcer, but this is by no means certain, because these symptoms may be due to hypermotility of the stomach which so frequently accompanies hypersecretion. Similarly, symptoms resulting from pyloric spasm due to emotional causes may be wrongly attributed to the hyperchlorhydria with which this condition is often associated. For the above reasons the term ' hyperchlorhydric dyspepsia ' cannot be recommended.

Management of dyspepsia.—When the family doctor is consulted for dyspepsia he should make a careful enquiry into the dietary history and social habits, as discussed in the opening paragraphs of this chapter. Thereafter he should make a general physical examination, including the abdomen. Unless he finds reason for suspecting some serious organic disease, it is unnecessary and probably unwise initially to investigate the stomach by a test meal or radiography. In most cases it will be found that the patient has been overworking or overworrying, or is bolting his meals or eating his meals when excessively tired, or has been smoking immoderately or taking too much alcohol. The patient should be assured that if he carries out the doctor's advice and takes a bland diet for a few days the dyspepsia will probably clear up rapidly. The summary of instructions given on page 824 may be of help to the doctor in reminding him of the various points of importance. A bland diet (Diet No. 3), made up from the foods permitted (p. 825) should be prescribed. If the dyspepsia fails to clear up or a relapse occurs within a short time, despite adherence to instructions, it is advisable to admit the patient to hospital where a full examination can be undertaken, including an investigation of the alimentary tract. If, on the other hand, the dyspepsia entirely disappears, the restrictions on foods which were initially imposed should be gradually relaxed. The patient with functional dyspepsia, gastritis or peptic ulcer who has been correctly treated should be able to eat almost any article of food, provided that he has learned to chew thoroughly and take plenty of time over his meals. It is undesirable and unwise for such patients to smoke excessively, to take alcohol on an empty stomach or to drink very strong tea or coffee. There is no real hardship in giving up pickles and taking condiments sparingly. On the other hand it is a real hardship both to the patient and his wife if he is *permanently* prohibited from taking soups or fried or fatty dishes. Again, such common articles as sausage, bacon and twice-cooked meats fill an important place in family diets. If eaten slowly, masticated well and taken in moderate quantities, they are well tolerated. Similarly, raw vegetables such as tender lettuce leaves and ripe tomatoes, and cooked coarse vegetables, should not be prohibited permanently. Common-sense avoidance of the coarse fibrous veins and the use of a sieve can make these valuable foods suitable for the majority of patients.

PEPTIC ULCER

Peptic ulcer is one of the most common diseases in civilised countries. It has been calculated from morbidity surveys that about one and a half million people living in Great Britain at the present time have suffered from this condition. Peptic ulcers may form in any part of the digestive tract which is exposed to acid gastric juice. They are commonly found in the stomach (gastric ulcer) or in the duodenum (duodenal ulcer) above the point of entry of the alkaline pancreatic juice. Occasionally they may be found in the lower end of the œsophagus or in the jejunum following gastroenterostomy, or in a Meckel's diverticulum associated with ectopic gastric mucosa.

The term ' peptic ulcer ' is used because it is widely believed that the ulcer arises from auto-digestion of the mucous membrane by the gastric secretions. How the healthy mucous membrane is protected from the action of gastric juice is little understood. Obviously a balance must exist between acid-pepsin secretion and mucosal resistance. Peptic ulcer never arises except in tissues exposed to acid gastric secretion. In patients with gastric ulcer the secretion of acid is often within normal limits, but patients with duodenal ulcer nearly always have a high output of acid. This is probably accounted for by the presence in the gastric mucosa of a larger than normal number of acid-secreting parietal cells and not by excessive secretion from a cell population of normal size. One of the factors predisposing to duodenal ulcer may be the inheritance of a stomach with a large number of parietal cells. The various factors determining the acid secretion by the stomach have been well reviewed by James (1957). He shows that in some people the stomach secretes large amounts of acid during the night, when it contains no food. This may be a factor contributing to the formation of peptic ulcer and it may prevent the healing of an ulcer once formed.

Relatively much less attention has been paid to the response of the gastric mucosa to its own secretion of enzymes and acid. One probable protective agent is the mucoprotein—mucin—which adheres to the stomach wall as a thin but resistant coating. Mucin is secreted by the gastric and duodenal glands in response to local nervous and hormonal influences. Sir Howard Florey (1955) in a Croonian lecture to the Royal Society has reviewed what is known about this protective action. It has been shown that mucin possesses no appreciable buffering power against hydrochloric acid and has no inhibitory effect on peptic digestion. Hence any protective action which it possesses probably depends on its acting, when gelled by contact with hydrochloric acid, as a physical barrier. Such a barrier would impede the mechanical mixing which brings the gastric juice in contact with the surface cells. The lubricant properties of mucin may also help to protect the mucosa from mechanical trauma. There is no satisfactory evidence that dietary factors play any part in upsetting the equilibrium between mucosal resistance and the digestive juice.

In the past there have been claims that dietary deficiencies cause peptic ulcer and these claims must be considered. They are based mostly on epidemiological evidence. The incidence of gastric ulcer and duodenal ulcer varies so markedly in different populations that they may be taken to be separate diseases. Certainly it is necessary to discuss them separately here. Two excellent reviews are available (Illingworth, 1953 ; Jones, 1957).

Gastric ulcer.—The chief argument to support the claim that dietary factors might be responsible for gastric ulcer is the fact that in Great Britain between the two wars it was between twice and five times as prevalent in the poorest class as in the upper social classes. The poorest social class at this time was consuming diets which were below physiological standards both in quantity and quality. Further, in recent years there has been a steady fall in the number of deaths attributable to gastric ulcer in men and in women. How much of this fall in mortality rates is due to improvements in the food consumed causing a reduction in the incidence of ulcers, or to improvements in treatment following new anæsthetics and increased surgical skill, is a matter of speculation. Gastric ulcer is rare in most parts of Asia and Africa, including many districts where the diet is known to be grossly defective. This fact makes it hard to credit the claim that dietary deficiency can have any part in the causation of this disease. Other explanations must be sought for the social class differences in Great Britain.

Duodenal ulcer.—In contrast to gastric ulcer, duodenal ulcer is uniformly distributed throughout the social classes in Great Britain. It is five to eight times as common in men as in women. A great increase during the past 50 years has been clearly established in many countries. Moreover, this increase has occurred during a period when the standard of living of the working classes has greatly improved in every respect. These facts suggest that nutritional deficiency is unlikely to be of importance in the ætiology of duodenal ulcer in Great Britain and other Western countries. Constitutional and other factors such as smoking, feeding habits, and the stress and competition of modern living require careful consideration. The possibility also exists, though proof is lacking, that modern methods of 'improving' and processing foodstuffs may alter their nutritional qualities or may add harmful constituents which may injure the stomach and duodenum.

On the other hand, in some parts of the world where the diet is poor, duodenal ulcer is very prevalent. South India is the most important example; it is also common in some districts in Indonesia and West Africa. Dogra (1940) made a very careful study in South India. He investigated 258 consecutive operations on cases of peptic ulcer at the Madras General Hospital. In all but five the ulcer was duodenal. He found that duodenal ulcer is almost entirely a disease of peasants and labourers, among whom all castes and creeds are affected in proportion to their numbers. It rarely occurs among the well-to-do. Similarly Sommervell and Orr (1936) found duodenal ulcer very common among the poor tapioca eaters in Travancore; yet they noted that it was rare amongst the fishermen, who presumably get plenty of protein from their fish. All these facts suggest strongly that in South India a poor diet is a contributory cause of duodenal ulcer. Nevertheless, in many other parts of the tropics where the diet is equally unsatisfactory, duodenal ulcer is not prevalent.

The South Indian by tradition eats his food very hot and heavily flavoured with spices and curries. It has been suggested that these might be responsible for duodenal ulcer. If this were so the well-to-do and the Brahmins, who eat very highly spiced food, might be expected to suffer most. Yet Dogra specifically states that duodenal ulcer is rare in these classes. The cause of the high incidence of duodenal ulcer in the peasants of South India remains quite unknown.

COFFEE, TEA, ALCOHOL AND TOBACCO.—Caffeine produces an increase in gastric secretion of a high acid content, and in large doses may cause marked hyperæmia of the gastric mucosa. Hence the possible harmful effect of strong tea or coffee. Alcohol has a similar effect, but it also stimulates the secretion of mucus and if taken repeatedly in excess in a concentrated form it may lead to acute damage to the superficial layers of the mucosa. Tobacco, especially cigarettes, contains various toxic substances besides nicotine. While smoking in moderation may relax the tone and abolish the hunger contractions of the fasting stomach, in excess it may cause nausea and vomiting. Its effect on gastric secretion appears to be variable. Since smoking appears to cause vasoconstriction of the vessels of the skin, it may have a similar effect on the blood vessels in the stomach. The assessment of the ætiological importance of these factors is very difficult because it is quite possible that individuals who are highly strung and constitutionally predisposed to the development of peptic ulcer may be the very people who would indulge excessively in drinking tea or coffee and in smoking.

OCCUPATIONAL FACTORS.—Certain occupations appear to predispose to peptic ulcers. Doctors are particularly prone and so are those in responsible positions in industry, such as foremen and business executives. It has been suggested that stress and strain and hurried and irregular meals with the consequent bolting of food and inadequate mastication might be important contributory factors. This may be so. If it is, one would expect a high incidence in bus drivers, who are submitted to long hours of strain and whose eating habits are reputed to be very irregular. Avery Jones (1957) and his colleagues have shown that bus drivers are not particularly prone to the disease. Agricultural workers were found to have a remarkably low incidence of duodenal ulcer.

CONSTITUTIONAL FACTORS.—There seems no doubt that in peptic ulcer there is a definite hereditary factor. In support of this view are the established facts that a high proportion of duodenal ulcer patients belong to blood group O, and that the close relations of ulcer patients are more liable to develop peptic ulcers than are the relatives of normal people. A strong family history is frequently found in patients who develop ulcers soon after puberty.

Conclusion.—From what has been said it is clear that the mystery of the ætiology of peptic ulcer remains unsolved. No satisfactory explanation is available either for the development of acute ulcers or for their failure to heal in a proportion of cases and hence to become chronic. The great increase in the incidence of duodenal ulcers in Great Britain and other Western countries which has occurred in recent times suggests that as a result of modern methods of living a loss of equilibrium has occurred between man and his environment. In predisposed people a variety of mechanisms or agents, as discussed above may contribute to the formation of acute ulcers or to a failure in their healing.

TREATMENT

Before discussing the medical and dietetic treatment of peptic ulcer it is necessary to indicate the types of case for which a surgeon should always be called into consultation. These types are :—

1. Old, indurated ulcers of the duodenum which are producing pyloric or duodenal stenosis and marked gastric retention, and gastric

ulcers on the lesser curvature producing such a degree of 'hour-glass' contraction of the stomach as to lead to obstructive symptoms.

2. Any gastric ulcer in middle-aged patients which does not show satisfactory signs of healing within 4 weeks while on strict medical treatment.
3. Ulcers of the pyloric antrum and pyloric canal, because ulcers at these sites are frequently malignant.
4. Ulcers which show a persistent tendency to bleed, in spite of repeated courses of medical treatment, and particularly if the patient is over 40 years of age and suffers from arteriosclerosis.
5. Ulcers which, despite medical treatment, cause recurrent attacks of dyspepsia sufficiently severe to lead to economic disability.
6. Perforation of a peptic ulcer.

Aims of treatment

The aims of medical treatment are threefold, namely the relief of symptoms, the healing of the ulcer and the prevention of recurrence.

Relief of symptoms.—In the absence of complications such as pyloric stenosis or penetration of the ulcer into adjacent organs, it is usually easy to secure relief of symptoms. In many patients the symptoms disappear spontaneously without any medical treatment; yet medical treatment usually leads to a more rapid and complete relief of the dyspepsia associated with both acute and chronic ulcers.

Healing of the ulcer.—The assessment of healing is obviously difficult. Radiological examination may show the presence of large ulcer craters although symptoms have ceased. In other words, healing and absence of symptoms are not synonymous. Assessment by gastroscopic examination presents considerable technical difficulty and repeated examinations are unpleasant for the patient; also gastroscopy is only of value in respect of gastric ulcers. The assessment of healing of duodenal ulcers is more difficult as it can be made only from radiological examination.

Since the majority of peptic ulcers have a natural tendency to heal, the assessment of the healing property of any remedy presents obvious difficulty. Nevertheless it seems reasonable to suggest that the treatment outlined below will not only help to secure relief of symptoms but may accelerate the rate of healing.

Prevention of recurrence.—This is an even more difficult problem. Patients have remissions and relapses with or without any treatment. Furthermore, any treatment given may work by suggestion rather than by any effect on the fundamental cause of the disease. Several studies over periods of years have failed to produce statistical evidence that medical treatment, either with drugs or diets, has any influence on the natural course of the disease. Consequently many forms of therapy which received widespread approval during the past 50 years are now discredited.

These difficulties make it important to treat every patient with an ulcer as an individual problem. Some relapse repeatedly despite medical treatment, including bed rest. For these patients surgery should be considered. In contrast, many patients remain for years either completely free from dyspepsia or suffer only mild symptoms which can easily be controlled ; obviously they can be allowed a more liberal regime. The decision regarding the duration of medical and dietetic treatment should be made not only on the severity of the patient's symptoms and on the situation of the ulcer, but on the assessment of the patient's temperament, occupation and social environment.

Patients who have the peptic ulcer diathesis should receive sensible advice about the possible harmful effects of hurried and irregular meals, of indigestible articles of food, particularly fried foods, of excessive smoking and excessive drinking of alcohol, tea and coffee, and the need for proper periods of rest for both mind and body. Such advice is more likely to be successful in the prevention of recurrences than reliance on drugs or special diets.

Principles of treatment

These are (1) rest, both physical and psychological ; (2) a bland diet, given in small amounts at frequent intervals ; and (3) drugs—sedatives, antacids and antispasmodics.

Before dealing with treatment in detail the importance of the acid and motor factors in peptic ulcer is briefly discussed.

The acid factor is of undoubted importance in the ætiology of peptic ulcer, since ulceration only occurs when hydrochloric acid is present in the stomach. In addition, duodenal ulcer is usually associated with a high acid output. It is widely held that excess hydrochloric acid is the most important factor in the prevention of healing of ulcers, and the chief object of nearly all recognised types of therapy is to reduce its secretion or neutralise its effect. We believe, however, that this aspect has been somewhat exaggerated, because when the ulcer has healed the acid content of the stomach may be as great as when treatment started ; also, many ulcers heal when a reorganisation of the patient's manner of living is affected, without treatment being given for the control of gastric secretion.

At the present time, however, it is probably wise to accept the view that hyperacidity tends to delay healing, and accordingly to utilise all the means at our disposal for reducing the secretory activity of the stomach and for neutralising, as far as possible, any excess of acid.

Motor factor.—Little is known about the effects of hypermotility in the causation and prevention of healing of peptic ulcer. Perhaps the motor activity is of more importance than the acid factor. Excessive and irregular peristalsis and pylorospasm may produce ischæmia and thus make the mucous membrane more susceptible to the action of hydrochloric acid and pepsin. Further, exaggerated muscular movements causing forcible impact of food against the lining of the stomach may damage the mucosa. Lastly, the motor factor is of importance when an ulcer has developed, since local rest for the attainment of healing is as important in the stomach as in any other situation in the body. Excess motor activity is often responsible for pain.

Rest, local and general.—With rest in bed for a period of 4 weeks many ulcers will heal satisfactorily even with an ordinary ward diet. It is always best to advise patients with proved gastric ulcer to go to bed for 4 weeks; often it is necessary to insist on this. For patients with duodenal ulcer, ambulant treatment with modified diets as discussed below may be given a trial in the first instance.

Rest in bed raises the powers of resistance of a patient who is suffering from physical exhaustion consequent on overwork in the office, factory or home. Rest is beneficial not only to the body as a whole but also locally to the stomach. Recumbency is important and ulcers in patients up and about appear to heal more slowly. There may be a mechanical effect of the upright position which may cause the full stomach to pull on its blood vessels and thus lead to vasoconstriction of the splanchnic circulation. Whatever the explanation, rest *in bed* is often of value. An ulcer regime is more effective in hospital, and the patient accepts more quickly and more easily the discipline and the inconveniences which he must undergo for a period of weeks when he may be feeling perfectly well. Lastly, he is removed from many petty causes of domestic worry and irritation, which keep up a state of nervous tension and must accordingly be controlled if satisfactory healing is to be obtained. Under such circumstances sedative drugs such as phenobarbitone are often of value. During the period of institutional treatment the physician can investigate the psychological factors of importance and aid the patient in making the adjustments in his social relations which may be necessary on his return to his home and work. At the same time education can be given with regard to eating habits, the types of food and drink to be taken and avoided, the harmful effects of smoking, the care of the teeth, etc.

The advantages of rest in bed are well known but it is not invariably essential or, in certain circumstances, even the best line of treatment for a patient with duodenal ulcer. For instance, if a married woman with three young children is admitted to hospital for treatment and is continuously worrying about whether the children are being properly looked after at home, better results may be obtained by treating the patient in her own house; in which case arrangements must be made for relieving her of some of her household duties, and thus enabling her to get modified rest. Again, if a patient with a duodenal ulcer is in fear of losing his employment because of being off duty for a period of one or two months, the resulting anxiety may more than counterbalance the benefits of rest in bed; in this case ambulant treatment with modified rest, arranged according to the individual circumstances, should first be tried, as it may be very effective. At the present time there are many more cases of duodenal ulcer treated in out-patient departments by ambulatory methods than are treated as in-patients in the wards, and the majority heal satisfactorily as judged by relief of symptoms and radiological examination. In view of these facts it is unwise to claim that rest in bed is essential, although it is probably desirable in many cases. We feel that, if ambulatory treatment is advised, it should be limited to cases of duodenal ulcer, since gastric ulcers, owing to their tendency to bleed or undergo malignant changes, require the most careful and repeated observation.

Diet in Peptic Ulcer

During the past 50 years innumerable schemes of diet have been advocated for the treatment of peptic ulcer. In all types the diet is bland and given in small amounts at short intervals. Since the percentage of good results claimed for each type of diet is approximately the same, it would appear that these two essentials are of more importance than the actual food constituents, which differ widely in the various schemes advocated. The diets used in the treatment of peptic ulcer can be classified into three main types: (1) The Sippy diet and its modification by Hurst consists essentially of hourly feeds of small quantities (150 ml.) of milk, cream or other milky food; (2) the Lenhartz diet, which is also given mainly in fluid form but contains more protein, supplied by eggs switched with milk; (3) the Meulengracht diet includes a much wider variety of foodstuffs, *e.g.* chicken, rabbit and other meats, fruits and vegetables, all the food being carefully pounded or sieved. The feeds are given at 2-hourly intervals.

It was claimed by the advocates of the Sippy type of diet that complete neutralisation of the hydrochloric acid in the gastric contents throughout the waking hours is obtained if, in addition to the hourly feeds of milk or milk pudding, antacids are given after, and atropine and olive oil before, some of the meals. More than 20 years ago Nicol (1939), working under S. D., demonstrated that this is not the case. In twenty consecutive patients suffering from peptic ulcer and hyperchlorhydria placed on this regime, from whom samples of gastric juice were removed at hourly intervals throughout the 24 hours, free hydrochloric acid was frequently present. The mean acidity obtained by averaging the figures for free hydrochloric acid in the twenty-four samples was actually higher in every case on this regime than when the patient was on 2-hourly feeds of the Meulengracht type or on four light meals a day. For this reason, and because of the inconvenience to patients and nurses of hourly feeds, we are satisfied that the intervals between feeds should be 2 hours and not 1 hour.

The chief difference between the Meulengracht and the Sippy types of diet is that the protein content is considerably higher in the former. Contrary to a common belief that protein should be restricted in ulcer diets because of its tendency to stimulate the secretion of hydrochloric acid, the giving of foods rich in protein, for example, pounded fish, chicken or eggs, reduces the hydrochloric acid much more efficiently and maintains it at a low level for longer periods than do meals consisting of milk and cream. The Meulengracht type of diet is more acceptable to the patient because it contains, from the beginning of treatment, a much wider variety of foods than either the Lenhartz or Sippy diet. Many of the foods allowed are given in the form of semi-solid purées, and this we have found to be of importance because they remain longer in the stomach than fluids, and hence are much more effective in neutralising and binding hydrochloric acid.

Meulengracht (1939) claimed, from his experience of 491 cases of peptic ulceration accompanied by severe hæmorrhage, that the lesions healed rapidly and effectively when treated by his methods. For many years we have treated patients suffering from peptic ulcer, with and without hæmatemesis, from the beginning with a modification of this type of diet. We can confidently recommend its use, both because of the excellent results obtained and because of the satisfaction given to patients and nursing staff.

First stage.—The speed with which peptic ulcers heal varies greatly, but it would be unwise to assume that, in general, a firm scar can be obtained in less than 2 months. We do not approve of ' step-ladder ' diets in which the amount of food is increased automatically at daily or weekly intervals. Such a method assumes that healing occurs at the same speed in every case. Accordingly, we advise a bland diet (Diet No. 4). This consists of seven small meals with adequate amounts of protein. In the great majority of cases of peptic ulcer such a diet supplemented with antacids and sedatives will lead to the disappearance of dyspepsia within a few days. In a small number of cases in which pain is severe and relief is not secured by the above measures, the patient should receive up to 6 pints (3 *l.*) of citrated milk daily, given intragastrically by drip. This completely neutralises the acid secreted by the stomach and pain is usually rapidly relieved. After two or three days the milk drip may be given between 8 P.M. and 8 A.M., while the bland Diet No. 4 can be taken during the day. When pain has been absent for two or three days the milk drip can be discontinued.

Care must be taken to see that the vitamin C intake is satisfactory. There have been many reports that patients with peptic ulcer excrete urine with very low levels of ascorbic acid. This has led to the view that ascorbic acid deficiency causes peptic ulcer. This is certainly wrong; it is the incorrect dietetic treatment of peptic ulcer that may cause ascorbic acid deficiency. Ascorbic acid is known to be essential for all healing processes. A properly constructed diet will ensure an adequate intake of vitamin C, which is provided by the fruit juice and fruit and vegetable purées in Diet No. 4.

Intermediate stage.—The diet recommended for the second month consists of the same articles of food given at the same intervals, but the quantities should be increased.

Post-ulcer regime.—This consists of an ordinary diet, but avoiding those foods in the list on page 824 which the patient has found from experience to cause dyspepsia. In addition he should never go longer than 2 to 2½ hours during the day-time without taking some food. This is accomplished by taking a glass of milk or milky food and a biscuit between breakfast and lunch, and between lunch and dinner, if he is not accustomed to taking tea, and last thing at night. This regime should be continued for at least two years and, better still, for life. At this stage drugs are unnecessary provided there are no symptoms.

If patients find that smoking leads to a return of symptoms, they should be encouraged to abstain permanently.

DRUGS.—Many drugs have been used for the treatment of peptic ulcer. While none has been definitely shown to have any effect on the natural course of the disease and on the prevention of recurrences, those described below have deservedly high reputations in relieving the associated symptoms and may accelerate healing.

1. SEDATIVES.—These may be very helpful in providing mental relaxation. For this purpose phenobarbitone is usually employed.

2. ANTACIDS.—Drugs commonly used are sodium bicarbonate, magnesium oxide, hydroxide and carbonate, calcium carbonate, aluminium hydroxide and magnesium trisilicate. These are usually effective in relieving the pain and should be prescribed for this purpose.

3. ANTISPASMODICS.—Belladonna and atropine inhibit gastric motility. They are useful in relieving pain, especially at night and if pylorospasm is present. They paralyse the vagus, and so also inhibit the secretion of acid and pepsin. New anticholinergic drugs, such as propantheline bromide, are now widely used. It is claimed by the manufacturers that they have a selective action and in therapeutic doses are active on the gastrointestinal tract without an equivalent potency on the heart and circulation. It is very doubtful if these newer drugs are more effective clinically than belladonna. They are more expensive.

COMPLICATIONS ASSOCIATED WITH MEDICAL TREATMENT

Excessive treatment is to be deprecated as it has sometimes led to undesirable results. Excessive intake of soluble alkalis can lead to alkalosis with tetany. Scurvy has arisen from too strict adherence for long periods to milk diets prescribed for ulcers. A rigid dietary regime may in obsessional persons give rise to emotional disturbances and so aggravate the symptoms. A condition (the milk-alkali syndrome) may arise in patients with renal or pulmonary disease who take large amounts of milk (more than 2 pints daily) and alkalis. Weakness and lethargy are the characteristic features and there may be psychological disturbances. Hypercalcæmia is always found and may give rise to calcification in the kidneys and elsewhere. Deaths have been reported. Fortunately all of these undesirable effects are very rare.

Pre-operative Complications

1. Hæmatemesis and melæna

The immediate medical treatment of bleeding from peptic ulcers consists of absolute physical rest in bed, the injection of morphia, the treatment of shock and the restoration of the blood volume by appropriate transfusion of blood and saline. This may mean in a case of even moderate severity the transfusion of 1·5 to 2 *l.* of blood and the same amount of glucose saline. If bleeding continues repeated transfusions may be necessary. All patients should be encouraged to drink water or citrated milk as freely as possible. In very ill patients with nausea and exhaustion who have no desire for food, it is unnecessary to force it on them ; for such collapsed patients, especially if they have continuing pain, in addition to intravenous infusion of glucose saline, citrated milk, 3 to 6 pints (1·5 to 3 *l.*) in 24 hours may be given through an intragastric tube (Chapter 48). Within a day or two milk, milky foods and egg and milk flips, about 5 oz. (150 ml.) at 2-hourly intervals, will be acceptable to the patient and will be adequate for the next 2 or 3 days. Thereafter the first-stage ulcer diet should be given.

For many years the orthodox treatment of gastrointestinal bleeding was the total exclusion of food and fluid by mouth. In 1931 Meulengracht, in Copenhagen, came to the conclusion that the withholding of food and fluid from patients who were suffering from post-hæmorrhagic shock was contrary to physiological principles. First, it failed to take into consideration the dire effect of shock which inevitably resulted from the reduction in blood volume and the serious effects of the losses of salt and water on the heart and kidneys. Secondly, it was based on the erroneous view that gastric rest was best obtained by the exclusion of food and fluid by mouth. Accordingly he adopted a method of treatment which permitted the patient to eat a varied and liberal bland diet *ad libitum* immediately after the hæmorrhage. He was satisfied that the good results obtained did not depend on any special diet, but on the supplying of adequate calories, protein, water, salts and vitamins. Meulengracht's opinion has been amply justified by experience in the last 30 years.

It should be remembered that the risk of death from hæmorrhage is markedly increased in patients over 55 years of age with chronic ulcers and who give a history of previous hæmorrhage, or in whom recurrent hæmorrhage occurs after admission to hospital. In such patients immediate removal of the ulcer by partial gastrectomy under cover of blood transfusion offers the best chance of recovery.

2. Perforation

An ulcer may perforate into the abdominal cavity. This is an acute surgical emergency. The orthodox treatment is to close the perforation if there is a short history of ulcer and a duodenal ulcer is present. For gastric ulcer, or if there is a history of recurrent pain for 2 years or longer, partial gastrectomy is usually advised. Post-operative treatment consists of allowing the patient to suck ice or sip water for 24 hours. On the second day small drinks of water or milk are allowed, and by the third day fluid or semi-fluid feeds are permitted. Within a week the patient should be taking the first-stage ulcer diet.

3. Pyloric obstruction

Peptic ulceration is frequently associated with pyloric obstruction. The obstruction may be due to cicatricial stenosis, to spasm or œdema, or to a combination of these features. Medical treatment consists of replacing losses of water and electrolytes which result from vomiting, by appropriate intravenous infusions, by aspirating the stomach contents night and morning, and by giving small feeds of citrated milk every 2 hours, or if pain and spasm are present and persistent, by the infusion during 24 hours of up to 6 pints (3 *l.*) of citrated milk through a tube introduced into the stomach. If medical treatment fails to relieve the clinical features of obstruction and if radiological examination suggests it is due to an organic cause, relief must be sought by operation, *e.g.* partial gastrectomy or gastroenterostomy. Pre-operative treatment may be required on the lines mentioned in the section devoted to cancer of the stomach.

POST-OPERATIVE COMPLICATIONS

1. The dumping syndrome

This develops commonly after gastrectomy, less frequently after gastroenterostomy and occasionally in normal people and people with peptic ulcers. The symptoms consist of a feeling of drowsiness, tiredness or fatigue, or muscular weakness. In addition there may be tachycardia and increased awareness of the heart's action. These may start at the end of a meal or within half an hour of its completion (the early post-prandial syndrome). The early syndrome is believed to be due to mechanical, thermal or chemical stimulation by food which has passed very rapidly out of the stomach and been ' dumped ' into the small intestine.

The symptoms of the late syndrome begin 1 to 1½ hours after a meal, especially if exercise has been taken ; they are weakness, tremor, faintness, hunger or an empty sensation in the epigastrium. Their probable cause is hypoglycæmia. During the first 6 weeks after gastrectomy some features of the dumping syndrome are present in the majority of patients ; by the end of 6 months less than 10 per cent. have residual symptoms sufficiently severe as to require treatment. The prevention and treatment of the early syndrome consists in taking time to meals, chewing the food thoroughly and lying down afterwards. Bulky meals must not be taken. Food and drink must be neither very hot nor very cold. By ensuring that meals contain ample fat and protein it is often possible to reduce the emptying rate of the stomach and thus prevent not only the symptoms of the early dumping syndrome but also the hypoglycæmic features which characterise the late syndrome. These may be relieved by taking sugar. In severe cases it may be necessary to augment the above dietetic measures by employing drugs which delay the emptying of the stomach. For this purpose anticholinergic drugs such as propantheline bromide have been found to be effective.

2. **Loss of weight**

Many patients lose weight after partial gastrectomy. The most likely causes of this are inadequate intake of calories because of the ingestion of insufficient quantities of food consequent on the reduced size of the stomach, and inadequate absorption of food, because of its rapid passage through the jejunum. As a rule the loss of weight is not severe and is of little significance except to persons who are engaged in heavy manual work. Such patients must be encouraged to eat frequently (six meals daily), to increase gradually the size of the meals and to ensure that each contains ample amounts of fat which is a concentrated source of calories.

3. **Anæmia**

While megaloblastic anæmia very rarely develops after partial gastrectomy, it occurs inevitably after total gastrectomy provided the patient lives long enough. Iron deficiency anæmia is exceedingly common, especially in women. This may cause much ill-health and a serious loss of economic efficiency which can be quickly and cheaply remedied by the administration of medicinal iron. All patients after gastrectomy should have their blood examined at least twice a year.

4. **Jejunal ulceration**

This may result when the jejunum is anastomosed to the stomach and thus becomes exposed to the effects of acid gastric juice. The medical treatment of jejunal ulcers is the same as that for duodenal ulcers. The results, however, are less satisfactory as the jejunal mucosa is even more susceptible than gastric or duodenal mucosa to the damaging effects of gastric juice. If medical, including dietetic, treatment fails to secure healing, recourse to further surgical treatment will be necessary.

GASTRITIS

The introduction of the flexible gastroscope, improvements in radiological technique and special methods of obtaining and fixing specimens for histological investigation have clearly demonstrated that gastritis occurs much more frequently than was formerly believed. The inflammatory lesion may be seen either in the acute phase (acute erosive gastritis) or in the chronic phase (chronic atrophic gastritis). Gastritis may result directly (1) from toxins, which reach the stomach via the blood stream ; these may be either of bacterial origin (*e.g.* influenza, pneumonia, pyogenic infections, etc.) or of metabolic origin (*e.g.* uræmia, diabetic coma) ; (2) by direct irritation of the mucous membrane of the stomach by ingestion of substances which are physical or chemical irritants (*e.g.* indigestible articles of food, alcohol, infected food and drugs such as salicylates, iodides, heavy metals) ; or (3) rarely, from foods to which the patient has a specific idiosyncrasy.

The clinical features of gastritis vary from mild anorexia, vague discomfort and heartburn, to severe and repeated vomiting accompanied by diarrhœa if there is associated enteritis. Sometimes the clinical picture may simulate that of acute peptic ulcer, and massive gastric hæmorrhage may occur in the absence of radiological evidence of peptic ulceration. Nausea, abdominal fullness, heartburn and pain occurring before breakfast and improving as the day goes on are frequently present in chronic alcoholics. Secretory studies indicate an outpouring of mucus and a reduction in the secretion of hydrochloric acid during attacks of acute gastritis and also in most cases of chronic gastritis. Yet chronic atrophic gastritis may give rise to no symptoms. It has been found, sometimes to a marked degree, at post-mortem of patients, who in life had made no complaint of dyspepsia.

An area of gastritis can often be found surrounding a peptic ulcer or cancer of the stomach. It is always difficult for a pathologist examining a specimen in which two disease processes are present to decide whether one gave rise to the other or if each had an independent origin. It is therefore not surprising that various authorities hold contradictory views on whether gastritis is a precursor of cancer or peptic ulcer or vice versa. Divergent views are also held on the ability of a stomach, the seat of chronic gastritis, to renew its damaged epithelium.

The long accepted view that the changes in the stomach in pernicious anæmia are the result of a genetically determined atrophy has recently been challenged by Magnus (1958). He claims from studies made during life, using a gastric biopsy tube, that the atrophy may arise as the final result of a progressive inflammatory gastritis. Atrophic gastritis has been shown by the same method to be present in half the patients suffering from severe iron deficiency anæmia. Recent evidence suggests that the gastric changes in pernicious anæmia may be due to a breakdown in the autoimmune processes of the body. Irvine *et al.* (1962) found complement fixing antibodies to an extract of mucosa of the body of human stomach in the sera of 75 per cent. of patients with pernicious anæmia, but in only 4 per cent. of sera from hospital control patients. The achlorhydria and the changes in parietal cells may be due to the destructive action of these antibodies.

Acute gastritis

The basic principles of treatment of a patient suffering from nausea, pain and vomiting due to a severe attack of acute gastritis may be summarised as follows :—

1. The neutralisation or removal of the causal irritant by the appropriate means, *e.g.* antibiotics, gastric lavage, antidotes for specific poisons.

2. The prescription of drugs, *e.g.* alkalis, bismuth and opium or one of its alkaloids, if acute intra-abdominal complications can be excluded.
3. The withholding of all solid foods for 24 to 48 hours.
4. The replacement of losses of water and electrolytes. Since acute gastritis with severe vomiting rarely lasts more than 2 or 3 days, attention need not be directed primarily to the maintenance of the patient's nutrition as is essential in chronic gastrointestinal diseases, but should be focused on the prevention of the serious complications of dehydration and the loss of electrolytes, associated with excessive vomiting.

While all food should be withheld, water or half-normal saline with or without the addition of glucose and fruit juice should be frequently given. Small amounts, 3 to 5 oz. (100 to 150 ml.) may be taken every hour. If the patient is unable to retain such fluids given by mouth, and signs of dehydration appear, normal saline or 5 per cent. glucose in normal saline must be given parenterally. With improvement of the patient's condition, small feeds of barley water, whey, or milk can be given ; thereafter the dietetic ladder can be gradually climbed by the addition of Benger's food, arrowroot, cornflour, custard and fruit jellies, until the first-stage dietary regime recommended for peptic ulcer and, later, a normal diet is reached.

Chronic gastritis

No matter whether chronic gastritis is associated with hyposecretion or hypersecretion of hydrochloric acid, the *immediate* underlying principle of treatment is the same, namely rest to the chronically inflamed gastric mucous membrane. The application of this principle may be summarised as follows : (1) removal or correction of the underlying causative factor, whether toxic, infective, physical or nervous in origin ; (2) correction of faulty habits of eating, drinking and smoking ; (3) administration of drugs—sodium bicarbonate, bismuth and magnesium carbonate, ferrous sulphate for iron deficiency anæmia and vitamin B_{12} for pernicious anæmia ; (4) the prescription of a bland diet given in small quantities, which is mechanically non-irritating and adequate in calories, minerals and vitamins (Diet No. 3). In most cases rest in bed is not required. When the cause has been removed and the symptoms of gastritis have disappeared, the patient can return to an ordinary diet provided he obeys the general instructions in regard to correct habits of eating, drinking and smoking.

CARCINOMA OF THE STOMACH

Carcinoma of the stomach is a very common form of cancer, especially in those over 45 years of age. It occurs in males more often than females.

The cause of gastric carcinoma is not known. Its relationship to chronic gastritis so strongly advocated by Hurst (1929) and others has been disputed by Magnus (1952) on the basis of his histological examinations of portions of stomach removed at operation. The evidence that dietary factors are of ætiological importance is unsatisfactory. The only form of successful therapy is radical surgical resection undertaken in the early stage of the disease before metastases have occurred. Unfortunately early diagnosis may be extremely difficult ; hence the poor results of surgical treatment when reviewed over a post-operative period of 5 years. Cancer may affect primarily the orifices or the body of the stomach. In the former case pain and vomiting with all its evil consequences on nutrition and salt and water metabolism are the principal features. Operative treatment is essential ; even when gastrectomy is found to be contraindicated, gastroenterostomy should be undertaken to relieve the obstruction. Pre-operative treatment is often desirable for a few days. This consists of washing out the dilated and inflamed stomach with saline and the correction of any electrolyte and water deficiency. In cancer of the body of the stomach, weakness, loss of appetite, vague abdominal discomfort and anæmia are the presenting features. Such patients are often diagnosed too late for radical surgery to be successful ; in which case treatment consists of giving the bland Diet No. 4 and the administration of iron for the correction of the anæmia.

DISEASES OF THE INTESTINES

The causes of diseases of the intestines may be classified under three groups.

1. **Inflammation.**—Examples are : (*a*) food poisoning due to a variety of organisms and toxic substances (Chapter 23) ; (*b*) enteric fever, dysentery and cholera ; (*c*) Crohn's disease (regional ileitis), non-specific (idiopathic) ulcerative colitis and diverticulitis, diseases in which the histological picture is that of a non-specific inflammation.

2. **Tumours.**—These may be simple (adenoma) or malignant (carcinoma). The small intestine is seldom involved ; in contrast the colon and rectum are frequently affected.

3. **Constitutional and psychological factors.**—Such conditions as megacolon (Hirschsprung's disease) and some cases of diverticulosis have been classified as constitutional diseases. Cœliac disease of infants and adults is now known to be due to a constitutional idiosyncrasy or sensitivity to wheat protein. Psychological disorders include spastic constipation, irritable bowel and nervous diarrhœa.

There is no satisfactory evidence to suggest that any of the above disorders are due to a deficiency of any known food factor. On the other hand they may cause malnutrition, dehydration and disturbance of electrolyte balance if malabsorption and diarrhœa are allowed to continue for more than a few days or in very severe cases for more than a few hours.

The outlook for diseases of the intestinal tract has greatly improved since the discovery of antibiotics and chemotherapeutic drugs and the acquisition of new knowledge of the ætiology and treatment of disturbances of the water and electrolyte balance ; also technical advances in anæsthesia have enabled major surgical procedures to be undertaken with remarkable safety even in elderly patients.

Predominant clinical features of diseases of the intestinal tract which may require dietetic treatment or special feeding methods (Chapter 48) are (1) diarrhœa, (2) malabsorption, (3) obstruction, and (4) constipation.

DIARRHŒA

Causes

Diarrhœa may be defined as the frequent passage of loose or watery unformed stools. It may be acute or chronic. It is necessary to point out that diarrhœa is a symptom, not a disease. Hence treatment must be preceded by a careful investigation of the cause.

The causes may be functional or organic. Functional diarrhœa results from neuromuscular overactivity consequent on emotional states. This is a common cause. Diarrhœa follows irritation or inflammation of the mucous membrane of the bowel by physical, chemical or bacterial agents. The most important cause of inflammation is bacterial infection, as occurs in ‘ food poisoning ’ (Chapter 23), dysentery and typhoid fever. In tropical and semi-tropical countries parasitic infection of the intestine, especially amœbiasis, should always be excluded. The most common cause of mechanical irritation is the passage into the colon of imperfectly digested food. Diarrhœa may be a prominent feature of organic disease affecting the small or large intestine, *e.g.* Crohn’s disease, the sprue syndrome, malignant disease, idiopathic ulcerative colitis. Diarrhœa may coexist with constipation, and result from the irritation of the mucous membrane by impacted hard fæcal masses.

Types of diarrhœa

For the recognition of the different types of diarrhœa a careful history should be taken, and naked-eye, chemical and microscopic examination of the stools made. When bacterial infection is suspected, the fæces should be sent to the laboratory for culture. Both for diagnosis and for assessing progress, radiological and sigmoidoscopic examinations may be required. Digital examination of the rectum should never be omitted if the cause of the diarrhœa is not apparent. By these means functional diarrhœa, in which the looseness of the motions is the only abnormality, can be distinguished from diarrhœa due to infection or inflammation, in which mucus, blood and pus are present. The appearance of the stool may indicate, from the consistence of the motions, the probable site of the lesion. If the stool is extremely watery, small intestinal hurry is probably present. If the lesion is in the colon the stool is usually thicker. A frothy acid stool suggests a failure of digestion of carbohydrate, and a foul alkaline stool indicates a deficient digestion of protein, while a clay-coloured or pale stool favours a diagnosis of steatorrhœa. By microscopic examination an excess of carbohydrate (as starch granules), protein (as undigested muscle fibres), or fat (as fat globules and fatty acid crystals) may be demonstrated in the fæces.

Treatment

Many patients consult their doctor for diarrhœa, when in reality they are suffering from constipation which they are treating with purgatives. Enquiry should be made into this possibility, and if cathartic drugs are being taken these must be stopped before investigating the cause and starting treatment.

Where diarrhœa is believed to be due to the ingestion of irritative material or bacterial or chemical toxins, it may be necessary to start treatment by washing out the stomach with saline or by giving a saline purge.

If the diarrhœa is functional in origin, psychotherapy is needed, and sedative drugs may be required.

If the cause is an infection, chemotherapeutic agents or antibiotics should be given such as sulphadiazine or chlortetracycline (aureomycin) for bacillary dysentery, and emetine for amœbic dysentery. When failure of digestion or absorption in the small intestine is the cause, the appropriate treatment is that given in the following section on the malabsorption syndrome.

Acute diarrhœa (from any cause).—The principles of treatment are as follows :—

1. Rest in bed and warmth are essential for severe cases.
2. The prevention and correction of dehydration and accompanying electrolyte imbalances. In severe diarrhœal diseases such as cholera, it is essential to give fluids and electrolytes by the parenteral route. Correction of potassium deficiency is particularly important.
3. The prescription of drugs for allaying inflammation, relieving colic, and reducing the excitability of the neuromuscular mechanism. For these purposes antibiotics, corticosteroids, bismuth carbonate, kaolin, atropine and opium or its alkaloids may be mentioned.
4. *Diet.*—In very severe cases it may be advisable, for a period not exceeding 48 hours, to give the patient nothing by mouth except water or, better still, half-normal saline (½ teaspoonful sodium chloride to 1 pint of water) flavoured with fruit juice and glucose. With improvement in the clinical conditions, very severely ill patients should be allowed to sip small quantities of the fluid as frequently as desired during the waking hours.

In less severe cases, treatment should start with 2-hourly feeds of 5 to 8 oz. (150 to 250 ml.) of one or other of the following : water, barley water or milk diluted with equal parts of water. With further improvement, which usually occurs within 24 to 48 hours, chicken broth, junket and custard, fruit and milk jellies, Benger's food, Ovaltine or Horlicks or other proprietary invalid foods, soft-boiled or scrambled eggs, refined cereals and milk puddings can be taken, and within a week the patient will probably be able to take the low roughage bland diet recommended for chronic dyspepsia (Diet No. 3).

Chronic diarrhœa (from any cause).—The general principles of treatment are as follows :—

1. Rest, both mental and physical, must be ensured, and the patient must not be allowed to become chilled.
2. Drugs may be necessary, as recommended above for acute diarrhœa.
3. A diet is prescribed which must be (*a*) adequate in calories and other essential nutrients. This is particularly important if the diarrhœa has been present or is likely to be present for a long time, and especially for children ; (*b*) given in small quantities at relatively short intervals ; (*c*) mechanically non-irritating and chemically non-stimulating. Coarse and indigestible foods containing much cellulose must be avoided and condiments, spices and fried foods prohibited. Food and drinks which are very hot or very cold should be avoided.

The objects are the prevention or correction of toxæmia, exhaustion, dehydration, anæmia and loss of weight. A mixture of foods rich in protein, minerals and vitamins must be supplied in ample quantities, while foods rich in fat and starches may be restricted, if not tolerated well.

For the majority of patients the well-balanced bland diet low in roughage (Diet No. 4) will be found satisfactory. The protein content can be increased by giving a supplement of the proprietary foods Casilan (Glaxo) or Lonalac (Mead Johnson). Additional supplements of vitamin C and the B complex may also be given.

Patients with ulcerative conditions of the colon should remain on a non-irritating, low residue diet until diarrhœa has ceased and blood and pus are absent from the fæces. The return to a normal diet should be carried out carefully and in slow stages, and it is probably wise for patients who have had ulcerative colitis to avoid foods known to be indigestible or to contain excessive amounts of coarse residue (see list on p. 824).

THE MALABSORPTION SYNDROME

Definition

A number of diseases are encountered in clinical practice in which the primary disorder is a defect of absorption of one or more of the necessary foodstuffs, mineral salts or vitamins. They are associated with some or all of the following features : abdominal distension, loss of weight, diarrhœa, anæmia, tetany and calcium and vitamin deficiencies. In the past some of these conditions have been called the steatorrhœas, since the difficulty of absorbing fat was the most evident single feature. It is essential to think of defective absorption in more general terms. Hence the title of ‘ the malabsorption syndrome.’ It can occur as a result of structural changes in the alimentary tract or its adjacent organs, or from a functional failure of absorption. There are several ways in which malabsorption may be brought about.

1. Failure of the food to reach the absorptive surfaces

If a gastro-colic or jejuno-colic fistula is present or for any reason a short-circuit of the alimentary tract or a large resection of the small intestine has to be done, food may not come sufficiently in contact with the absorbing surfaces. Treatment is surgical. After operation a bland nutritious diet must be prescribed which may require to be supplemented with minerals and vitamins, as indicated in each individual case.

2. Failure of digestion

Digestion is a necessary preliminary to absorption and it may be impaired, particularly in diseases affecting the pancreas. Thus the malabsorption syndrome may develop in adults with chronic pancreatitis and in children with congenital cystic disease of the pancreas. In chronic diseases of the pancreas the defective secretion of diastase, trypsin and lipase leads to a failure in digestion and hence to the absorption of carbohydrate, protein and fat. The treatment of pancreatic diarrhœa is discussed on p. 510. Occasionally the secretion of one enzyme may apparently be deficient.

Carbohydrate intolerance.—If a patient suffering from diarrhœa, abdominal discomfort and flatulence passes motions which are frothy and strongly acid in reaction, this condition should be suspected. It has been given the name ‘ intestinal carbohydrate dyspepsia.’ Infants and young children especially may not tolerate too much carbohydrate in their diets. The diagnosis will be confirmed by finding in the fæces large numbers of starch granules. With intestinal hurry undigested starch passes rapidly into the colon, where it is fermented and the acids formed irritate the mucous membrane. More rarely intestinal carbohydrate dyspepsia is due to a deficient secretion of diastase. The treatment consists of the exclusion or reduction of starchy food from the diet. The monosaccharides and disaccharides in the form of glucose, cane-sugar, honey and jam are allowed. Bread, toast, scones, pastry, potatoes, green peas, lentils and root vegetables are either excluded from the diet or reduced in quantity depending, upon the severity of the condition. In the majority of cases a slice of crisp toast or one or two rusks can be taken with safety at breakfast and tea. As the condition improves, starchy foods should be slowly increased. Taka-diastase tablets (Parke & Davis), which contain starch-splitting enzymes, may be of value in enabling additional amounts of starchy food to be taken. In severe cases codeine is useful in retarding small intestinal hurry.

Putreactive diarrhœa.—A failure in the digestion of protein is indicated by the presence of dark, foul-smelling stools in which muscle fibres may be recognised under the microscope. Under these conditions beef, mutton, chicken, liver and kidney should be prohibited. Protein should be provided by dairy products, *i.e.* milk, cheese and cereals. Cereals and vegetables need not necessarily be restricted as carbohydrate digestion may not be impaired.

Steatorrhœa.—Excess of fat in the stools may be due to an absence of bile from the intestine because of obstruction of the biliary passages, a failure in secretion of lipase by the pancreas, or defective absorption of fat from the bowel, as occurs in structural disease of the small intestine and in tropical and non-tropical sprue (cœliac disease and idiopathic steatorrhœa).

Since steatorrhœa is a feature of many diseases and disorders of the gastrointestinal tract, treatment must be preceded by accurate diagnosis. This may be easy or very difficult, and may entail the carrying out of a variety of tests (radiological, chemical, hæmatological) and the undertaking of special measures for establishing the presence of absorptive defects. In all forms of steatorrhœa the essential dietetic method of controlling the diarrhœa is by reducing the fat intake.

It is best to begin with a diet which is as nearly fat-free as possible, and to add small quantities of fat every few days until the patient's limit of tolerance is reached. The following articles of food are particularly rich in fat and should be rigorously excluded at first :—

All fried foods.
All foods made with much butter, lard or margarine, *e.g.* pastries, pies, sauces, suet puddings and cakes.
All visible fats of meat, whether beef or mutton.
Fat meats such as pork, duck, goose, ham, bacon, sausages.
Fat fish such as salmon (tinned or fresh), mackerel, herrings, sardines.
Olive oil, mayonnaise, cod-liver oil.
Nuts and all sweets and cakes containing nuts.
Chocolate and cocoa.
Toffee, caramels and marzipan.

Of all fat, milk fat is best tolerated ; hence the first fatty food to be added to the diet is milk.

Pancreatic diarrhœa.—When the steatorrhœa is due to chronic pancreatitis or carcinoma of the pancreas, the dietetic treatment of the diarrhœa and the associated loss of weight may be extremely difficult as defects in the digestion of carbohydrate and protein are also usually present. Nevertheless it is from these two food constituents that the diet has mainly to be constructed, because the principal cause of the diarrhœa is the steatorrhœa. All food rich in fats must be strictly prohibited (see above). Milk should be given skimmed. Small amounts of crisp toast, rusks and cereals are permitted. A small helping of chicken, white fish or very lean meat is allowed at lunch and dinner, with any vegetable (except fried potatoes). Fruits (fresh or stewed), jams, jelly and sugar should be taken plentifully. Diet No. 5 will be found suitable for the initial treatment of chronic pancreatic deficiency of moderate severity. If the patient is seriously ill, he may not be able to take a diet as large as this at first. For a few days it may be necessary to omit some of the solid foods. It will then be desirable to give extra protein ; Casilan (Glaxo) or Lonalac (Mead Johnson) are suitable proprietary preparations of dried milk proteins and can be added to the milk or other beverages. Supplements of the fat soluble vitamins A, D and K and the B group of vitamins should be given to all cases with a history of long-continued diarrhœa.

The deficient secretion of the pancreas may be helped by substitution therapy. Pancreatin (B.P.) is a preparation containing the pancreatic enzymes. It is available in tablets or capsules covered with a protective coating resistant to the hydrochloric acid secreted by the stomach. It should be given in large doses before and after meals.

When the fatty diarrhœa has been brought under control, the caloric content of the diet must be increased gradually by allowing larger helpings of fish, chicken and lean meat, and by including, cautiously, additional amounts of fat in the form of fresh milk and small amounts of butter or margarine.

3. Diversion of foodstuffs by intestinal organisms

It has been known for a long time that intestinal organisms can synthesise certain vitamins, especially those belonging to the B group. More recently it has been shown that under certain circumstances an abnormal intestinal flora can divert to its own use substances (*e.g.* cyanocobalamin) which are essential for the health of the body and which are only needed in minute amounts. Infection of the small intestine with the fish tapeworm can produce a similar result.

A clinical example of this phenomenon is the so-called ' blind loop ' syndrome. In general, the bacterial flora in a cul-de-sac off the gut produces no ill-effects. Under certain conditions, however, there develops within this cul-de-sac or the ' blind loop ' a growth of bacteria which, by diverting to its own use cyanocobalamin and probably other trace substances, leads to a form of megaloblastic anæmia associated usually with steatorrhœa and other evidences of malabsorption. For the same reason an abnormal bacterial flora developing in multiple jejunal diverticula can also lead to the same syndrome.

4. Failure of the absorptive mechanism

This may be due to: (*a*) Organic disease in the wall, lacteals or lymphatics of the small intestine, *e.g.* in abdominal tuberculosis, Crohn's disease, Hodgkin's disease, amyloid disease, carcinomatosis, etc. The treatment in this group consists of the administration of appropriate antibiotics, steroid therapy and, in suitable cases, surgical resection. In all cases a bland nutritious diet is advocated, which to begin with should be relatively low in fat.

(*b*) In cœliac disease, idiopathic steatorrhœa and tropical sprue a defect in absorption may be present in the absence of obvious gross pathology. This is the most important group of all numerically. Histological examination of biopsy specimens of the jejunum has shown that mucosal atrophy is usually present, but whether this is the cause or the result of the malabsorption in the sprue syndrome is not clear.

Tropical Sprue

Sprue is the name which the Dutch in Java gave to a tropical disease in which the presenting features are sore mouth, fatty diarrhœa and associated secondary manifestations of subnutrition and malnutrition. The cause is unknown.

Although delayed and defective absorption of fat is the abnormality most easily recognised, the absorption of water, sodium chloride, glucose, vitamins and minerals is also impaired. The absorption of amino acids is less affected and the excretion of pancreatic enzymes is normal. This is important when constructing diets suitable for the treatment of sprue.

The disease is widespread in the tropics, especially in some parts of Asia, but is very rare, if it occurs at all, in Africa. The classical form is found most frequently in Europeans. Though sprue occurs in Indians, Chinese, Malays and Negroes, it is much less common in these races. This may be because of the absence of some genetic trait or because their usual diets contain much less fat than European diets, and in consequence the characteristic fatty stool is seldom seen.

It is also interesting to recall the absence of sprue in British soldiers who were prisoners of war in Japanese camps and whose daily intake of fat was as low as 5 g. a day, and the high incidence of sprue in soldiers of the same race fighting with the Chindit force in Burma under similar environmental conditions, but subsisting on the American 'K' ration which was very rich in fat.

Sprue usually attacks Europeans who have been long resident in the tropics. Yet a newcomer, whose diet and state of nutrition are both excellent, may develop the disease after only a few weeks residence.

The discovery that gluten is the agent responsible for cœliac disease (p. 514) indicates the possibility that some constitutional inability to deal with certain nutrients may be important. Thus it has been suggested that the explanation of the geographical location of tropical sprue in Ceylon, India, Java and China and its absence in tropical countries such as Africa, may be correlated with the foods eaten in these different regions. In India unsaturated vegetable fats are frequently used in the cooking of food. These fats have a tendency to become rancid and hence irritate the mucosa of the small intestine. On the other hand, in Africa the fats used are derived mainly from palm and coconut oil.

Tropical sprue sometimes occurs in epidemic form, as in the British troops serving in Burma. The hill stations in India deservedly acquired a reputation as centres for sprue and 'hill diarrhœa.' For this reason it has been postulated that sprue may be due to an infective agent. It is difficult to sustain this thesis. Extensive searches have been made by many bacteriologists for a specific infective agent and none has been found: if indeed one exists, it must be a virus or some agent which has defied orthodox methods of isolation and identification. An attack of sprue frequently follows upon either bacillary or amœbic dysentery, but the association with those two diseases has not survived statistical analysis (Woodruff, 1949).

There appears to be no association with climatic stress; indeed, as already stated the disease is common in the hill stations with their excellent climate, and is absent in equatorial Africa with a climate similar to that of parts of Asia where the disease is common.

There is thus no certainty as to the cause of Asian tropical sprue. There is, however, no doubt that the diarrhœa, loss of weight, vitamin deficiencies and anæmia result from a failure of intestinal absorption and not from a primary dietetic deficiency.

Sprue is a serious disease, and without proper medical and dietary care may prove fatal. Remissions and relapses are common. With proper treatment the majority of patients make a full recovery and seldom relapse, particularly if they leave the tropics. Nevertheless a few fail to respond to all forms of therapy and become chronic invalids.

Treatment.—The objects of treatment are the restoration of function of the alimentary tract, and the correction of demonstrable deficiencies. The principles of treatment may be summarised as follows: (1) rest in bed; (2) the administration of vitamins and minerals, if there is evidence of a deficiency, *e.g.* the vitamin B group (especially folic acid) for glossitis, stomatitis and megaloblastic anæmia; calcium for hypocalcæmia and tetany; iron for anæmia (vitamin K if a hæmorrhagic state is present); (3) the prescription of a diet which is mechanically non-irritating, high in protein and low in fat and carbohydrate, as originally recommended by Hamilton Fairley. Diet No. 5 is suitable for a case of moderate severity. In severe cases the fat may be further restricted by giving skimmed milk and taking great care to give only lean meat. Lastly, for the few cases which fail to respond to the above measures, short courses of treatment with a slowly absorbed sulphonamide, such as succinylsulphathiazide, 10 g. daily, alternating with chloramphenicol or chlortetracycline, 1 to 2 g. daily, may greatly reduce the diarrhœa.

The degree of carbohydrate restriction will vary from case to case, and can be assessed clinically by the symptoms of abdominal discomfort and distension and by the amount of frothy fermentation and acidity of the stools. This dietetic regime has largely superseded the milk diets, raw meat diets and fruit diets which have been recommended in the past.

For a discussion of the treatment of anæmia in the malabsorption syndrome see Chapter 43.

NON-TROPICAL SPRUE

A syndrome clinically indistinguishable from tropical sprue occurs in children and adults who have never resided in the tropics. Such cases can be placed in one of four groups : (1) Cœliac disease of infants and adults ; this is due to an idiosyncrasy or sensitivity to the gluten of wheat and is by far the most important group numerically. (2) Organic disease of the wall, lacteals or lymphatics, extensive resections, short-circuiting operations, fistulæ and blind loops of the small intestine. (3) Pancreatic disease leading to a failure in digestion, especially of fats (p. 510). (4) Idiopathic steatorrhœa in which no cause can be found and for which the treatment is that of tropical sprue.

CŒLIAC DISEASE OF CHILDREN AND ADULTS

Cœliac disease is now known to be a gluten-induced enteropathy. Jejunal biopsy invariably shows atrophy of the villi.

Credit for the discovery that an idiosyncrasy or sensitivity to gluten is the cause of cœliac disease must go to the Dutch workers, Dicke (1950) and Weijers (1950). It was soon confirmed in England (Anderson *et al.*, 1952).

Gluten is a mixture of proteins (p. 66) and it is now known that gliadin is the component responsible for cœliac disease.

The inflammatory reaction in the mucosal cells of the small intestine caused by gliadin produces cellular injury and a massive secretion of mucus which interfere with absorption, especially of fat, but also of vitamins, minerals, carbohydrates and proteins. Most of the fat in the stools is present in the form of free fatty acid.

Cœliac disease usually begins in childhood within the first three years of life. The child fails to thrive and loses appetite, and is characteristically pot-bellied. Dwarfing and infantilism gradually develop ; the stools are large, pale and offensive due to the presence of an excess of free fatty acids. Before the discovery of the value of gluten-free diets, about one-third of the children died, one-third recovered completely, and in one-third the disease continued into adult life. It is now known that many cases formerly described as idiopathic steatorrhœa were in fact cases of mild cœliac disease which were recognised for the first time in adult life. The clinical features of adult cœliac disease are indistinguishable from those of tropical sprue except that they are often more severe in degree, and prior to the discovery of the gluten-free diet they were less amenable to treatment.

Treatment.—The disease can be *completely* relieved if gluten derived from wheat or rye is *entirely excluded* from the diet. This is a formidable task for wheat flour is present in bread, many breakfast cereals, biscuits, cakes and pastries, sausage, macaroni and spaghetti ; it is added to many soups, sauces and puddings and also to some proprietary milk preparations such as Ovaltine. Gluten is absent from cornflakes, oatmeal porridge, rice and all fruits and vegetables, and also all meats. These foods are permissible.

Fletcher and McCririck (1958) have given a valuable account of how to overcome the difficulties of preparing gluten-free diets. Besides long lists of forbidden and acceptable foods, there is a table setting out those processed foods which the manufacturers state contain no gluten.

Gluten-free flour (wheat flour from which all gluten has been removed) may be obtained in 7 lb. tins from Energen Foods Ltd., Pound Lane, Willesden, London. Bread made from gluten-free flour is available in most large towns. It can also be obtained from Birkett and Bostock Ltd., Dept. T.R.D., Coronation Bakery, Stockport, Cheshire.

Diet No. 6 gives a sample menu for a day.

Children who have suffered from cœliac disease for a short time respond to the gluten-free diet within a few weeks. Patients who have been ill for years, and this is particularly the case when the disease attacks adults, may have a very badly damaged mucous membrane. Such patients require 3 to 6 months dietetic treatment before improvement becomes apparent. While awaiting recovery the following instructions should be followed.

If the patient is seriously ill, rest in bed and careful nursing are essential. As fats and also perhaps carbohydrates are poorly tolerated, it may be necessary to begin treatment with a diet confined to skimmed milk. Five daily feeds of 6 to 8 oz. (180 to 250 ml.) may be given. Fruit juices are usually well tolerated. The caloric intake may be increased by thickening the milk by adding milk protein (Casilan—Glaxo or Lonalac—Mead Johnson) and by sweetening the fruit juice. Progress may be slow and adversely affected by infections.

Gradually other foods may be added, preferably one at a time to each meal, *e.g.* fruits, especially bananas, lightly boiled eggs, minced meat and liver, fish, vegetable purée, junkets and jellies, sweets, honey and jam and later cheese and butter. Fried foods should be avoided until recovery is complete.

Anæmia is present in most patients with cœliac disease. In more than 90 per cent. of children it is due to iron deficiency and in the remainder folic acid deficiency is usually the cause. In adult cœliac disease, a megaloblastic anæmia due to folic acid deficiency is frequently present. Correction of both types of anæmia will occur coincidentally with the improvement in absorption which results from the gluten-free diet. Until this recovery is complete, it is advisable to give iron orally and in some cases parenterally to those patients with hypochromic anæmia, and folic acid by mouth to those with a megaloblastic anæmia. These preparations will cure not only the anæmia but the glossitis and stomatitis which may also be present.

The remarkable success which results from the gluten-free diet in both children and adults suffering from cœliac disease can only be obtained if every trace of gluten is eliminated from the diet. The gluten-free diet must be continued for 12 to 24 months after the stools have returned to normal and a satisfactory gain in weight achieved. Thereafter a cautious return to gluten-containing foods may be made. In a letter to us Sir Wilfred Sheldon states that of eighty-five children with cœliac disease who had been successfully treated on a gluten-free diet and then allowed a normal diet for a minimum period of 2 years, fifty-five remained well. Of the other thirty, sixteen showed many of the old manifestations of their disease and fourteen failed to grow satisfactorily. It would appear that after a long period of strict treatment (about two or three years), children may be allowed to return to a normal diet, but their further progress must be checked carefully at regular intervals.

In adults with cœliac disease the outlook for complete recovery is not so good. Dr J. M. French (personal communication) states that eight patients who had responded well to a gluten-free diet all became ill when gluten was given as a test. In some the relapse was so severe as to necessitate a return to hospital. Clearly, great care is needed when any adult is allowed to experiment with a return to normal food.

Intestinal Obstruction

Intestinal obstruction may be caused by many different pathological conditions. It is essential to decide in every case whether the cause of the obstruction is mechanical or due to paralysis of the intestinal muscle (paralytic ileus), as treatment in each type is entirely different. It is also desirable to determine whether the obstruction is high, *i.e.* in the jejunum or upper ileum, or low, *i.e.* in the lower ileum or colon, and whether strangulation of the bowel has occurred.

The common causes of mechanical obstruction are external hernias, volvulus, tumours of the colon, and bands or adhesions due to previous inflammatory disease or operation, and in children, intussusception. Paralytic ileus is usually a consequence of peritonitis, resulting from any cause, *e.g.* a gastric or intestinal perforation or an abdominal operation.

The chief features of intestinal obstruction are vomiting, complete constipation, and colicky pain which may be absent or slight in paralytic ileus. A serious loss of water and electrolytes results from the vomiting and from the stagnation of intestinal secretions in the dilated paralysed loops. The loss of fluid from the circulation from this latter source may be several litres in the 24 hours and this may lead to extrarenal uræmia. The accompanying loss of potassium is an important factor in the production of the apathy, mental confusion and muscular weakness, which usually follows intestinal obstruction.

Intestinal obstruction is always serious and so it should be treated only in a hospital where surgical and biochemical help are available.

Immediate operation is required for the relief of mechanical obstruction, while it is strongly contraindicated in paralytic ileus. In the latter type of obstruction the distension of the paralysed gut must be treated by continuous suction through a tube passed into the stomach or better still into the jejunum. Suction may have to be continued for a period which may last from 2 to 3 days to 2 to 3 weeks, depending on the time it takes for the bowel to recover from its paralysed state. In both types of obstruction the loss of fluid and electrolytes must be made good by appropriate infusions and special feeding methods may be required (see Chapter 48).

COLITIS

Inflammation of the colon may be due to specific infection with many different agents, the most important of which are (*a*) bacterial, *e.g.* the *Shiga*, *Flexner* or *Sonne* members of the genus *Shigella*, which cause bacillary dysentery ; (*b*) protozoal, *e.g. E. histolytica*, the cause of amœbic dysentery ; and (*c*) helminthic, *e.g. S. mansoni.*

In addition, mention must be made of the disease called non-specific or idiopathic ulcerative colitis, in which no specific organisms have been isolated despite the fact that the microscopic and naked eye appearance of the inflammatory and ulcerative changes in the colon are indistinguishable from those of bacillary dysentery. While the specific inflammatory disorders respond to treatment with appropriate chemotherapeutic agents and antibiotics, the same cannot be said of non-specific ulcerative colitis. The tendency of this disease to remit and relapse irrespective of what treatment is prescribed is notorious. Nevertheless, much can be done by skilled nursing and medical care (including psychotherapy) and by symptomatic treatment to bring the patient successfully through a relapse or prepare him for surgery. The fæcal loss of fluid, electrolytes and blood must be made good and every attempt must be made to maintain nitrogen balance.

While sulphonamides and antibiotics have proved disappointing in the treatment of non-specific ulcerative colitis, corticotrophin and the corticosteroids are of great symptomatic value in reducing the inflammation of the colon and hence the degree of diarrhœa, in improving the appetite and in inducing an optimistic outlook and a sense of well-being. For those patients with non-specific ulcerative colitis who fail to respond adequately to medical treatment and for those who frequently relapse with bouts of diarrhœa, fever and general ill-health, the operations of ileostomy and colectomy usually produce dramatic improvement.

For all types of colitis, specific or non-specific, the general therapeutic measures and dietetic treatment for diarrhœa, as outlined on page 508, are all of value.

DIVERTICULOSIS AND DIVERTICULITIS

Diverticula are blind pouches which may be present in the œsophagus, stomach and small and large intestines. They may be congenital in origin or be acquired during life. They are found most frequently in the colon, and especially in the sigmoid section. The presence of diverticula is known as diverticulosis ; when they are inflamed the condition is called diverticulitis. Diverticulosis is a very common finding and it is estimated that 5 to 10 per cent. of all persons have diverticulosis, and of these only 5 or 10 per cent. develop diverticulitis. Colonic diverticula develop in middle-aged and elderly people, many of whom are obese. Stagnation occurs in diverticula and if this is followed by infection an inflammatory reaction occurs which changes the disorder from diverticulosis to diverticulitis. Repeated attacks of diverticulitis result in a chronically inflamed bowel, with narrowing of the lumen and pericolic adhesions.

Treatment.—If symptomless diverticula are discovered during a routine radiological examination, no treatment is required and the patient should not be informed of their presence.

Many cases of diverticulitis have periodic attacks of mild left-sided abdominal pain, fever and irregularity of the bowels. These should be treated medically by antispasmodics, antibiotics and diet. Many of these patients are obese ; in which case weight-reducing diets should be prescribed. The diet should be constructed to prevent constipation, and yet at the same time it must not contain excess of roughage. For this purpose fruit and green vegetables are suitable, provided they are carefully sieved and served as purées. To increase the bulk of the intestinal contents Agar-agar, a product derived from seaweed, or psyllium, a product of vegetable mucilage, should be given, supplemented by the lubricant, liquid paraffin. The foods listed on page 824 as unsuitable for all cases of dyspepsia should be avoided or taken sparingly. The bland diet (Diet No. 3) will be found suitable. Purgatives should not be used. If constipation occurs despite the patient following and adhering to the general instructions given on page 520 and taking the diet and supplements discussed above, a mild laxative such as milk of magnesia or a glycerine suppository should be tried.

For a minority of cases surgical intervention will be required for features of obstruction, perforation or abscess formation, or for severe and extensive involvement of the intestine.

CARCINOMA OF THE COLON AND RECTUM

While carcinomas are rare in the small intestine, they occur in the large intestine with a frequency second only to that of the stomach. Sarcomas also occur in the large bowel but are far less common.

Ætiology.—As elsewhere in the body, search has been made for a pre-cancerous condition. The only diseases known to be associated with cancer are ulcerative colitis, when it has been present for many years, and multiple polyposis. There is no established association between carcinoma and diverticulitis.

Pathology.—The most common site for cancer of the large bowel is the rectum, with the sigmoid, cæcum and ascending colon next in order of frequency. There is a different symptomatology of carcinomas of the descending and ascending colon. Carcinomas of the descending colon tend to produce obstruction, while cancer of the ascending colon is usually associated with symptoms of toxæmia from absorption through the ulcerated growth. Very important is the symptom of altered bowel habit in the form of increasing constipation or diarrhœa, or an alternation of both.

CONSTIPATION

For comfort and health, most people require a daily bowel movement. However, since good health may be maintained by people who defæcate only once every 2 or 3 days, it is unwise to insist that a daily bowel motion is always essential. While both sexes and all age groups may be affected by constipation, multiparous middle-aged women, people living sedentary lives, and those who are confined to bed, are especially predisposed to the condition. Constipation may be due to organic disease such as mechanical or paralytic obstruction of the intestines, or to general diseases or diseases not connected with the alimentary tract, *e.g.* myxœdema, lead poisoning, mental depression, excessive sedation, but these causes are much rarer than the functional disorders discussed below. In clinical practice the term ' constipation ' is used to denote the chronic types due to colonic stasis and rectal stasis (dyschezia).

The chronic ill-effects of constipation have probably been exaggerated ; nevertheless evacuation which is insufficient and infrequent is often associated with symptoms such as malaise, headache, coated tongue, foul breath and mental sluggishness. The harmful effects of constipation have been ascribed in the past to the absorption of toxins from the fæcal material in the colon. As evacuation of the bowel usually gives prompt relief from these symptoms, such a cause is unlikely. A more probable explanation is that the pressure of the fæcal mass on the nerve-endings in the colon and rectum initiates afferent impulses which lead to the symptoms characteristic of the overloaded intestine.

The harmful effects ascribed to constipation are due to its treatment by over-purgation. The frequent passage of watery stools may lead to a depletion of potassium and sodium and the production of abdominal pain and flatulent dyspepsia.

Delay in the passage of the fæces may occur :—

1. In their movement along the large intestine—colonic stasis

The movement of the fæces along the intestinal canal is involuntary and is dependent on an adequate muscular power of the intestinal wall, properly stimulated to peristaltic activity by suitable food residue. Colonic stasis may be due to : (*a*) Weakness of the musculature of the intestinal wall ; this frequently develops in later life as a result of old age, debilitating disease, the long-continued ingestion of a faulty diet or the excessive use of chemical purgatives. This type of constipation is often called *atonic* constipation. (*b*) Spasm of the colon, leading to a retardation of the forward movement of the intestinal contents—*spastic* constipation. (*c*) Abnormal consistency of the fæces : for easy expulsion, the colonic contents must be semi-solid, and to produce fæces of this character the food must contain a sufficiency of cellulose. Concentrated foods which are almost completely digested and absorbed may give a fæcal mass which is small and hard, and so difficult to pass. The taking of insufficient amounts of fluid daily is another factor which may lead to the formation of hard, dry fæces.

2. **In their evacuation from the pelvic colon and rectum—dyschezia**

The desire to defæcate is caused by the entry into the rectum of the fæces which have accumulated in the pelvic colon. The passage of the fæces from the pelvic colon to the rectum is brought about by a mass peristalsis of the colon, which is stimulated by the entry of food into the stomach (gastro-colic reflex) or by the morning activities of getting up.

Dyschezia may be due to :—

(*a*) Faulty habits with regard to time or regularity of going to stool.

(*b*) Depressed reflex sensitivity. If the subjective desire for defæcation is habitually neglected, the sensory impulses set up when fæces enter the rectum are less effective. This is also found in association with psychological disorders.

(*c*) Weakness of the voluntary muscles of defæcation (the diaphragm, the abdominal muscles and the muscles of the pelvic floor).

Treatment

Before starting treatment it is essential to take a careful history and make a full clinical examination so as to exclude organic diseases which can lead to constipation. The second step is to discuss with the patient the mechanisms which may lead to constipation, including the use of purgatives ; and the third step is to allay his fears in regard to its reputed ill-effects.

Although it is advisable to consider the treatment of atonic and spastic constipation separately, there are certain common principles which are applicable to the prevention and treatment of fæcal stasis in general.

1. **The prevention and correction of faulty habits.**—The basis of constipation is frequently laid in infancy and childhood by lack of insistence on the part of the mother on a regular timetable for going to stool. The same lack of training may arise in school children or in adults from a failure to answer nature's call whether due to laziness, hurry or lack of sufficient lavatory accommodation. Once the reflex resulting from the entrance of fæces into the rectum is lost, it can only be regained with difficulty by persistent and unhurried attempts to move the bowels at the same time every day whether the desire to defæcate is present or not. The

patient must also establish a correct attitude of mind towards the problem. The influence of worry, anxiety, alteration of occupation and fatigue are factors which may affect the normal rhythm of evacuation. This must be pointed out to the patient.

2. **The taking of adequate physical exercise.**—This is an important factor in treatment, and applies equally to the obese person and to the thin individual with an anxiety neurosis and a spastic colon. Regular exercise (walking, cycling, riding, rowing, golfing, etc.) in the open air, supplemented if necessary by ' exercises ' for the development of the abdominal muscles, should be recommended and graded according to the age and physical state of each individual.

3. **Removal of painful causes,** *e.g.* anal fissures should be treated surgically.

4. **Diet.**—The foods which are of particular value in the treatment of constipation are :—

(*a*) Those which contain adequate amounts of cellulose. Since cellulose is not digested by enzymatic or bacterial activity, it enters the colon as a mixture of semi-solid consistency and stimulates peristaltic activity by its bulk and by its mechanically irritating properties. The refining of cereals by milling, with the resultant loss of cellulose in the bran reduces the bulk of the fæces and so leads to constipation. Therefore in prescribing a diet for constipation, wholemeal cereals should replace the more finely milled cereal products. The leafy vegetables (cabbage, spinach, lettuce, etc.) and the roots (carrots, turnips, onions, etc.) are also valuable sources of roughage and vitamins. It is unwise to prescribe initially an excessive amount of vegetables to a constipated patient who has been accustomed for years to a low residue diet, as the colon cannot be expected to adjust itself suddenly to such a rapid change. At first, vegetables should be given in moderate quantities at two meals and should be sieved and served as purées. In the spastic form of constipation the quantities given should be progressively increased, and a coarser sieve used, until the vegetables can be taken raw or cooked in the ordinary way without sieving.

(*b*) Fruit, fresh and cooked, is of great value, containing as it does roughage in the form of cellulose. The quantity eaten daily should be increased gradually until a good serving is taken at two meals a day at least. In the initial stage of treatment of atonic constipation and throughout the treatment of the spastic variety, it is often desirable to exclude raw fruit such as apples and pears and to rely on cooked fruit which has been sieved, and on prunes, fruit juices and fruit jellies. As with vegetables, an attempt should be made to increase steadily the quantity of raw fruit eaten and to desist from the use of sieving subsequent to cooking.

(*c*) Reference has already been made to the importance of taking plenty of fluid to help to keep the fæces soft ; six to eight glasses of fluid (up to 2 *l.*) should be taken in the 24 hours. The great value of the glass of water, particularly if hot, before breakfast has long been recognised. When the stomach and small intestines are empty, the water passes rapidly down to the colon and excites the peristaltic movements.

Diet No. 7 is suitable for the treatment of atonic constipation and incorporates the above principles. When obesity is present, Diet No. 1 may be prescribed.

5. **Drugs.**—For the treatment of chronic constipation reliance should be placed essentially on the correction of faulty habits and the prescription of a proper diet as described above ; drugs should play only a minor role. Cathartics such as castor oil and calomel are contraindicated, but it may be necessary to use mild vegetable laxatives (senna, cascara sagrada, etc.) for a period in patients in whom constipation has been present for years. Inert substances which lubricate the bowel content (liquid paraffin) or add bulk to the fæces (agar-agar, psyllium) are often of value.

FUNCTIONAL DISORDERS OF THE GASTROINTESTINAL TRACT

Apart from its nutritive value, food acquires psychological connotations and the giving of food is symbolic of friendship and love in all countries of the world. A wide variety of gastrointestinal features such as dysphagia, dyspepsia, loss of appetite, painful spasms, constipation and diarrhœa can be expressions of a psychological disorder.

Globus Hystericus

The sensation of a ' lump in the throat ' is not infrequently complained of by persons suffering from grief or some emotional disturbance. It is due to spasm of the upper sphincter of the œsophagus and is sometimes called ' globus hystericus.' It should be treated by explanation and reassurance, and if possible the removal of the psychological cause.

Functional Dyspepsia

Functional or nervous dyspepsia is a term used to describe a condition in which dyspeptic symptoms are present, but there is no evidence of any structural disease. The symptoms arise from a disordered control of the alimentary canal by the higher nervous centres and are a manifestation of anxiety neurosis.

Functional dyspepsia may be associated with the whole range of gastric acidity from achlorhydria to hyperchlorhydria and radiological examination may show hypermotility, normal motility or a hypotonic state of the gastric musculature. When there is excessive gastric secretion and motility, the clinical features may be similar to those of peptic ulcer. With hypoacidity and gastric atony, nausea, discomfort and heaviness in the stomach after meals are sometimes the chief symptoms.

The diagnosis depends on two factors : (1) the demonstration of an anxiety state, attributable to overwork, worry and excessive fatigue, whether physical or mental; and (2) the exclusion of organic disease in the alimentary tract and its adjacent organs. For this purpose it may be necessary to examine the appendix, the gall-bladder and the colon as well as the stomach by the appropriate physical and laboratory tests since it is well recognised that dyspepsia can be caused by reflex effects from these organs.

Treatment is by psychotherapy and diet. Psychotherapy includes the effects produced on the patient by taking a careful history of his digestive troubles and of the family and other worries, and the making of a complete physical examination. To quote Alvarez, " From the mental purgation that results from pouring out worries and from receiving sympathetic advice, great benefits ensue." The cause of the anxiety or mental tension must be discovered and removed or, if this is impossible, the patient must be persuaded to accept it with understanding.

The principles on which the dietetic treatment are based have already been set out under the general management of dyspepsia. For the majority of patients the bland Diet No. 3 will be found to be satisfactory. For the minority of patients, if the symptoms are very severe, rest in bed for a few days may be of value.

Sedatives, antispasmodics and antacids may be required for symptomatic treatment.

[illegible] the hig[illegible] [illegible]g individu[illegible] [illegible]sed by the passage of loose stools after meals or as a result of some situation producing emotional strain. The sufferer may become so conscious of, and so obsessed with, his condition that visits to a theatre or travel in a train without access to a toilet become impossible. There are no abnormal physical signs beyond those of general reactivity such as tachycardia and brisk reflexes. Examination by barium enema and sigmoidoscopy are normal.

After organic disease has been excluded, the doctor should discuss the condition with the patient and reassure him. Phenobarbitone may help him to avoid some of the effects of an emotive situation, and codeine in doses of 15 mg. (1/4 gr.) is a most helpful drug in aiding the patient to regain control of his bowel activity. At first it is taken 1 to 3 times a day as required until the motions are formed. Tablets should be carried by the patient [illegible] [illegible]fidence and [illegible]

ANOREXIA NERVOSA

A functional disorder which may cause grave ill-health or even death is called anorexia nervosa. Anorexia may be defined as a loss of the general desire to eat without dividing this desire into its component factors of hunger, appetite and food habit. Anorexia of mild degree is a common symptom of anxiety neuroses and is not infrequently encountered in psychotic states. The term ' anorexia nervosa ' should be restricted to the syndrome in which the loss of appetite is severe in degree and is conditioned by a hysterical reaction.

The type of patient to develop such a hysterical reaction is one who is emotionally immature and unstable and usually highly suggestible. The psychological disturbance is often repressed into the subconscious mind and is replaced by a physical symptom.

The patient is usually a young unmarried woman. In some cases the exciting cause may be easily discovered, *e.g.* a desire to slim, or a childish method of attracting attention. Occasionally there seems to be a mental association between the idea of getting fat and that of becoming pregnant. In many cases the underlying cause, being deeply repressed, is difficult to elicit. The distaste for all foods is complete, and if the patient is forced to take food it may be vomited. The patient may go to extreme lengths to conceal food which she is supposed to have eaten at table, and which is afterwards thrown away. Following the anorexia there is loss of weight which may be extreme, but it should be noted as of considerable diagnostic importance that there is little change in physical or mental activity until very late in the disease. Other clinical features are an associated amenorrhœa and a downy growth of hair on the body.

Treatment is best carried out in a hospital or nursing home. Psychological treatment should be undertaken with the object of persuading the patient to eat. In many cases this can be carried out by the physician, but if the disorder lies deep in the subconscious mind, the opinion of a psychiatrist should be sought. It should be emphasised to the patient that she has [illegible] the eating habit, and that the desire for food will not [illegible] loss of app[illegible] be expressions of a psychological disorder. [illegible] fact grows by what [illegible]

Globus Hystericus

The sensation of a ' lump in the throat ' is not infrequently complained of by persons suffering from grief or some emotional disturbance. It is due to spasm of the upper sphincter of the œsophagus and is sometimes called ' globus hystericus.' It should be treated by explanation and reassurance, and if possible the removal of the psychological cause.

Functional Dyspepsia

Functional or nervous dyspepsia is a term used to describe a condition in which dyspeptic symptoms are present, but there is no evidence of any [illegible] disease. The symptoms given [illegible] designate the [illegible] of the types such as spastic colon, ' mucous colitis,' nervous diarrhœa, but it is probably better to admit their unity of origin and to accept all such manifestations as examples of the syndrome of the ' irritable bowel.' The term ' mucous colitis ' is particularly unfortunate, as the condition is emphatically not an inflammation of the colon. The behaviour of the colon is only part of a general picture of autonomic disturbance which may affect the whole gastrointestinal tract, and indeed the whole body.

Sufferers from irritable colon are almost invariably unstable and emotional middle-aged women who gradually develop a ' constipation complex ' and are inveterate takers of cathartics. In such patients the colon when in a spasm can be palpated through the abdominal wall, and the spastic condition can be confirmed by radiological examination.

The essential principles of treating the irritable colon associated with spastic constipation are :—

1. Psychotherapy.
2. The use of sedative and antispasmodic drugs (phenobarbitone and belladonna).
3. The avoidance of purgatives and colonic lavage.
4. The use of a bland, highly nutritious diet which is low in roughage. Diet No. 3 is suitable. It is essential to reduce the roughage, initially at least, as its presence irritates the colon and increases spasm. The fæcal bulk necessary to promote peristalsis may be obtained from agar-agar, a product derived from seaweed (two heaped teaspoonfuls of powdered agar thrice daily after meals) or from the vegetable mucilages (*e.g.* psyllium), while liquid paraffin is of value as a lubricant. An attempt should be made at suitable intervals gradually to increase the intake of fruit and vegetables.

Nervous diarrhœa.—In contrast to spastic constipation, the patient with an irritable bowel may suffer from the disorder called nervous diarrhœa. This condition occurs in the highly strung individual and is characterised by the passage of loose stools after meals or as a result of some situation producing emotional strain. The sufferer may become so conscious of, and so obsessed with, his condition that visits to a theatre or travel in a train without access to a toilet become impossible. There are no abnormal physical signs beyond those of general reactivity such as tachycardia and brisk reflexes. Examination by barium enema and sigmoidoscopy are normal.

After organic disease has been excluded, the doctor should discuss the condition with the patient and reassure him. Phenobarbitone may help him to avoid some of the effects of an emotive situation, and codeine in doses of 15 mg. ($\frac{1}{4}$ gr.) is a most helpful drug in aiding the patient to regain control of his bowel activity. At first it is taken 1 to 3 times a day as required until the motions are formed. Tablets should be carried by the patient. Soon the patient will regain his confidence and can reduce the frequency of administration. Finally he may only require to take a tablet on occasions known to be associated with particularly severe emotional stress. This treatment very rarely fails.

During the initial stages of treatment the patient may require to take a bland diet low in roughage (Diet No. 3), but a gradual return to a normal diet should be the aim of dietetic treatment.

CHAPTER 39

DISEASES OF THE LIVER AND BILIARY TRACT

ANATOMICAL CONSIDERATIONS

On microscopical examination the liver appears to be made up of a series of lobules. In the centre of each lobule is a branch of the hepatic vein. These drain the blood from the liver and lead it into the systemic circulation via the inferior vena cava. At the periphery of the lobules the branches of the portal vein can be seen ; these bring the blood to the liver cells from the abdominal viscera. Running with the portal veins are branches of the bile duct and hepatic artery. The liver cells are arranged in columns radiating out from the hepatic vein at the centre of the lobule to the portal system. These considerations are important, because some pathological processes start around the centre and others around the periphery of the lobules. Excellent accounts of many aspects of liver disease are given by Maclagan (1957), Popper and Schaffner (1957) and Sherlock (1958).

DIET AS A CAUSE OF DISEASES OF THE LIVER

The major portion of the nutrients in the diet after digestion are absorbed into the portal vessels and carried by the portal vein first to the liver. Any poisonous substance in the diet after absorption is similarly transported first to the liver. The liver is responsible for some 25 per cent. of the basal metabolism and is intimately concerned with the metabolism of carbohydrates, protein, fat and vitamins. It also plays an important role in the activation of hormones and the detoxication of drugs. That a bad diet can contribute to disorders of the liver is beyond dispute. The complexity both of human diets and of liver functions make the subject of the relation between diet and liver disease in man extremely difficult. Before discussing possibilities and theories—which may have important practical applications for health—it is best to consider the evidence of the relation of diet to hepatic disorders, which has been obtained from experimental animals. There are facts that have been well established in the laboratory and these provide essential information on which to base a discussion of human pathology.

EXPERIMENTAL PRODUCTION OF HEPATIC DISEASE IN ANIMALS

Three types of hepatic disease can be produced in the laboratory—fatty degeneration, necrosis and cirrhosis. Necrosis may be a slow process imposed on fatty degeneration, or there may be an acute massive necrosis. In certain circumstances both fatty degeneration and necrosis can lead to extensive fibrosis of the organ with the characteristic picture of cirrhosis of the liver.

Fatty degeneration.—Before the discovery of insulin, it was well known that diabetic patients readily developed fatty degeneration of the liver ; after the discovery of insulin, the Toronto school found that dogs made diabetic by total pancreatectomy, but maintained on adequate doses of insulin, developed after a few months fatty changes in the liver. These arose first around the portal vessels. The rate at which these changes occurred depended in part upon the diet. Certain diets were found to possess lipotropic properties, which enabled the fat in the liver to be mobilised and thus prevented the fatty changes. A large number of studies, which have been reviewed by Best *et al.* (1956), showed that choline is an important lipotropic factor. There is no evidence that choline is an essential nutrient or a vitamin, but under a variety of circumstances in experimental animals, choline added to the diet can prevent the accumulation of fat in the liver.

Gyorgy and Goldblatt (1939) in Philadelphia, Himsworth (1950) in London, and others have produced fatty changes in the livers of rats by diets low in protein. It is probable that the protective action of protein on the liver is due in large part to the sulphur-containing amino acids, especially methionine. As a source of labile methyl groups, methionine may be essential for the synthesis of choline in the body. Other factors appear to protect the liver against these changes. Of these the most important is probably vitamin E. The characteristic fatty changes in the livers of rats fed on diets low in protein occur only if the diets are also low in vitamin E.

Fatty changes in the liver of experimental animals can also be brought about by a large number of toxic chemicals, including many substances such as chloroform and carbon tetrachloride which have been used in medicine and in industry. A poor diet low in protein can make the liver more susceptible to chemical poisons. These fatty changes are distributed in the peripheral cells around the portal system.

Necrosis.—Fatty degeneration, if severe, may lead to necrosis of the parenchymatous cells of the liver. Occasionally experimental animals on diets low in protein develop a generalised acute necrosis of the liver. This is usually fatal, but recovery may take place.

Cirrhosis.—Fatty degeneration may heal with the formation of fine scar tissue either around the portal tract or the central hepatic veins. In either case cirrhosis of the liver results. Occasionally massive necrosis of the liver may heal and a large area of fibrous scar tissue replaces the damaged liver cells. A coarse cirrhosis of the liver is thus formed.

There is thus no doubt that in experimental animals a number of pathological conditions can be produced in the liver by dietary means. These can only be produced consistently if great care is taken in the construction of the diets. The casein in particular must be carefully purified.

DIET AND LIVER DISEASE IN MAN

Alcohol.—The regular consumption for a long time of alcohol, either as wine or spirits, frequently leads to liver disease. Fatty degeneration of the liver is common amongst alcoholics and not a few develop a diffuse portal cirrhosis (Laennec's cirrhosis). The intense scarring of the liver impedes the portal circulation and the pressure rises in the veins draining the abdominal viscera. The combination of increased portal pressure and hypoproteinæmia may cause large quantities (many litres) of fluid to accumulate in the peritoneal cavity (ascites).

It was natural to attribute the pathological changes in the liver to the direct toxic effect of alcohol and at one time this was the accepted teaching. Second thoughts have arisen owing to the following facts. In experiments on animals it has been shown that alcohol is not very toxic to the liver. As already described in Chapter 7, the human body is able to metabolise considerable quantities of alcohol daily without harmful effects. Indeed some heavy drinkers appear to maintain their health and to suffer no liver damage for many years. Whether this is due to some constitutional superiority of the individual's liver or to eating a good diet while drinking heavily, is a matter of speculation.

The diet of many alcoholics is known to be unsatisfactory in many ways. The large number of calories provided by the alcohol may depress the appetite for other foods or the appetite may be affected by chronic gastritis or hepatitis. Alcoholism frequently leads to poverty and money may not be available for the purchase of an adequate diet. The protein intake of many alcoholics is certainly well below acceptable standards. It is a reasonable hypothesis that the liver changes in many alcoholics arise as much or more from a lack of protein and other nutrients in the diet as from the direct toxic effects of alcohol.

Important therapeutic implications obviously stem from this hypothesis. In the treatment of alcoholic disease of the liver it is essential to ensure that a well-balanced diet is taken with plenty of protein. It would, however, be foolish to consider the condition solely as a simple dietary deficiency and to ignore the toxic effects of alcohol. Although alcohol may not be as powerful a hepatic poison as it was once thought to be, there can be little doubt that it exerts some deleterious effects.

Protein malnutrition.—It is certain that after weaning an inadequate supply of protein of good quality in the diet leads to extensive fatty degeneration of the liver. This has already been described and discussed in Chapter 28 dealing with the disease kwashiorkor. Wherever kwashiorkor is endemic, the livers of children who do not suffer from overt forms of the disease and who appear apparently healthy, may present histological changes. Some increased fat, cellular infiltration and fine scarring are often found in biopsy material. Yet it is known that livers with severe fatty degeneration attributable to kwashiorkor may heal completely and subsequently on biopsy present a normal histological picture. Stein and Isaacson (1960) report that Bantu children of Johannesburg, amongst whom protein malnutrition is common, suffer no more from cirrhosis of the liver than do children in other countries with a vastly superior nutritional background. However, Chanda (1958) in Calcutta studied the histology of the livers of thirty-four children who had died of kwashiorkor. In four of these livers he found fully developed cirrhosis ; he claims to have demonstrated the evolution of cirrhosis from fatty changes. It seems probable that when protein malnutrition is associated with heavy loads of parasites or severe infection, a degree of liver damage may result which would be unlikely to develop if only one of these factors was operating. This is discussed further in the next paragraphs. Much more information is required about the after-effects of malnutrition, especially an inadequate protein intake, in causing liver damage both in adults and in children.

Tropical cirrhosis of the liver

Whereas in Great Britain, consequent upon the decline of alcoholism, it is not unusual to make a ward round in a large hospital and see no patient with cirrhosis of the liver, this is not so in the tropics, where patients with portal cirrhosis of the Laennec type with ascites are frequently encountered. This is not usually attributable to alcoholism. The patients may be of any age and of either sex, but men between 20 and 40 years are most frequently affected. Although cirrhosis of the liver is a well-known problem to clinicians working in hospitals in Africa, Asia and Latin America, there is little reliable information about the extent of the disease or its ætiology or epidemiology.

When it was discovered that in experimental animals fatty degeneration of the liver, produced by poor diets inadequate in protein, could develop into cirrhosis, it was natural to think that a similar sequence could happen in man. The view became widely held that tropical cirrhosis of the liver was a sequel to a long period of fatty degeneration of dietary origin. It is now clear that the situation is not as simple as this. While it is true that in small-scale maps of the world the areas of incidence of kwashiorkor and cirrhosis of the liver appear to approximate closely, in large-scale maps of smaller areas agreement is not nearly so close. Thus Walters and Waterlow (1954) found that in Gambia cirrhosis was very common, but fatty changes in the liver were seldom seen. They noted that malaria was hyperendemic in the area. On the other hand van der Sar (1951) has reported that fatty changes in the liver were common in Curaçao, but there was no undue incidence of cirrhosis. Similar anomalies have been reported in other parts of Africa and Latin America.

Waterlow and Bras (1957) have therefore suggested that " deficient diets, such as are eaten by people in underdeveloped countries, may have an *indirect* effect on the liver ; they may predispose it to injuries by other noxious agents—toxins, parasites and viruses, according to the *genius loci.*"

This hypothesis, which as they point out is not new, is receiving much general support and a theory of dual ætiology of cirrhosis reconciles many discrepancies.

The number of possible noxious agents is great. Alcohol has already been discussed. The possibility of malaria causing permanent liver damage has been the subject of dispute for at least a century. The concept that repeated attacks of malaria may act on a liver impaired by a poor diet and so lead to cirrhosis is consistent with the observations of Walters and Waterlow. Another important agent is the virus responsible for infective hepatitis. The virus is widespread in the tropics and there is evidence that in certain tropical areas the resulting disease is much more serious than that usually seen in Europe. It is not unreasonable to suppose that in some patients tropical cirrhosis has arisen as a sequel to infective hepatitis.

Environmental factors in the tropics are so diverse that it is probably unwise to attempt to give a precise statement of the ætiology of hepatic disease. Perhaps the French writer Charmot (1954), who has considerable experience of diseases of the liver in Dakar, comes as near the truth as is possible. He attributes the fundamental cause of liver cirrhosis in West Africa to an existence which is filled with ignorance, misery, malnutrition, to the absence of good food and hygiene, and to infestation with a multitude of parasites.

Veno-occlusive disease of the liver

Workers in Jamaica have described a pathological condition not hitherto recognised. In the fatty degeneration associated with protein malnutrition and in tropical and alcoholic cirrhosis of the liver, the pathological processes begin around the portal veins at the periphery of the liver lobule. In Jamaica a condition is not uncommon in which degenerative processes start around the hepatic veins in the centre of the lobule. Occlusion of the hepatic veins may occur owing to thickening of the intimal lining ; venous drainage is thus impaired. Cirrhosis may follow with the scarring distributed around the central veins in the lobules. Sometimes branches of the hepatic vein are blocked by clots. Bras and Hill (1956), who give an excellent account of the disease, show that its pathology is quite different from that of portal cirrhosis.

Clinically, the distinction of veno-occlusive disease from other types of liver disease is less clear. Jelliffe, Bras and Stuart (1954) described an acute stage characterised by a sudden onset of abdominal distension due to liver enlargement. Ascites, often massive, is usual, but jaundice and an enlarged spleen are not often present. A child may decline rapidly and die in coma from liver failure in a few days. Some children, however, appear to make a complete recovery. Alternatively, the disease may enter a subacute stage, characterised by firm, smooth enlargement of the liver. There is often recurrent ascites and other evidence of venous obstruction. This stage may also be followed by complete recovery. More often, after periods of clinical improvement, a final stage develops which is indistinguishable from other types of cirrhosis. Ascites, splenomegaly, dilated collateral veins, jaundice and hæmatemesis may all be present. The mortality is high.

The ætiology of the disease presents interesting problems. It may occur at all ages, but is perhaps most common in children. Few of the patients have been well fed previously, but the disease is not associated closely with obvious physical evidence of malnutrition, and it is certainly not a sequel of fatty degeneration associated with protein malnutrition.

The view is now widely held in Jamaica that the condition arises as a result of poisoning by ' bush teas.' In the island a great variety of plants and herbs, at least a hundred species, are used for making teas and medicinal drinks. The pharmacological properties of these drinks have not yet been systematically studied. Clinical histories have been recorded which are quite consistent with the theory that veno-occlusive disease of the liver arises from drinking bush teas. As, however, a large proportion of the population, including the young children, drink some form or other of bush tea, it is very difficult to get clear-cut evidence of an association between the disease and drinking infusions of a particular herb.

Herbs of the genus *Senecio* are known to contain a toxic alkaloid which acts on the liver ; in experimental animals, and also in horses and cattle, these herbs have produced liver damage with microscopical appearances very similar to that of veno-occlusive disease in man. There is evidence that other herbs have a similar effect. A poor diet might well sensitise the human liver to the action of toxins derived from herbs.

Infantile biliary cirrhosis

This is a disease of India. The pathology was described in a classical paper by Radhakrishna Rao (1935), and a more recent report of an authoritative committee (Indian Council of Medical Research. Liver Disease Sub-committee, 1955) is also available. The characteristic lesion is a diffuse liver necrosis without fatty degeneration, but with obliterative lesions of the terminal divisions of the hepatic veins. Cirrhosis subsequently develops. There is a high mortality.

The disease is widespread in India. All observers are agreed that it occurs mostly in the middle classes ; thus it is not associated with poverty or gross malnutrition. Waterlow and Bras have examined tissues from India and report that the histological changes are very similar to chronic veno-occlusive disease as observed in Jamaica. This, however, is denied by Amarjit Singh and his colleagues (1961), who made a clinical and pathological study of 114 children with cirrhosis of the liver in North India.

A new approach is suggested by the report of Balasubrahmanyan and Chopra (1960), who found heavy deposits of copper in the liver cells obtained by needle biopsy from children with infantile cirrhosis, but not in liver cells from adult cirrhosis. They suggest that it is time to start

Dietitian

investigating possible causes other than the much discussed toxic, infective and nutritional factors.

Cirrhosis of the liver and iron

The rare disease hæmochromatosis is due to a congenital fault in the intestinal barrier against iron (Chapter 11). Excessive amounts are absorbed and deposited in the tissues, including the liver. Cirrhosis is liable to develop after a number of years. In South Africa, Bantus frequently have a large amount of iron in the tissues, including the liver (siderosis), as already described in Chapter 11 ; this is probably in part due to an excessive iron intake derived from the iron cooking vessels and also perhaps to a breakdown of the intestinal barrier, secondary to malnutrition. Since cirrhosis of the liver is common in Bantus, this excess iron may be a contributory factor. Bothwell and Bradlow (1960) have studied the iron content and histological appearance of the livers of Bantus who had died accidental deaths. They found an association between the concentration of iron and the presence of portal cirrhosis ; a marked degree of cirrhosis was found in eleven specimens in which the iron content was over 2 per cent. (normal value 0·1 per cent.). The question is still under discussion.

Cancer of the liver

Primary cancer of the liver is very rare in Europe and North America. It is much more common in many parts of the tropics. No specific carcinogenic agent has yet been reported : indeed it is unlikely that one will be found. Cancer of the liver probably arises as a result of a variety of causes producing liver damage and leading to cirrhosis of the liver. If cirrhosis of the liver could be prevented or much reduced in the tropics, it is probable that cancer of the liver would become as rare there as elsewhere in the world.

PARENCHYMAL DISEASE OF THE LIVER DUE TO INFECTIONS AND TOXIC AGENTS

INFECTIONS.—Hepatic damage may occur in many diseases caused by bacteria, protozoa, spirochætes or viruses. The liver is, however, especially affected by leptospirosis (Weil's disease), yellow fever and infective hepatitis. Except in yellow fever zones, the last disease is by far the most important. Although there is no evidence to show that susceptibility to contracting any of the diseases mentioned above is increased by malnutrition, there is good reason to believe that their hepatoxic effects may be augmented by any preceding condition which leads to hepatic damage, *e.g.* protein deficiency in the diet, alcoholism or the degenerative effects which accompany advancing age. Infection of the liver can occur in one of four forms. First, it may be so mild that it is not recognised clinically and can only be diagnosed by laboratory tests. Secondly, and this is the most common, the illness is of moderate severity. Complete recovery is the rule in the vast majority of such patients, but the time taken varies from a few days to many months. Thirdly, and very occasionally, the clinical course from the onset may be that of subacute or acute necrosis of the liver, death usually occurring within a few days or weeks. Fourthly, and again rarely, the final pathological result may be portal cirrhosis (chronic hepatitis).

Hepatoxic agents.—These include many substances, especially organic solvents and heavy metals, used in industry. Carbon tetrachloride, a solvent for dry cleaning, window cleaning and many other industrial processes, is perhaps the most important. Many drugs, some in common use, occasionally cause hepatic damage, *e.g.* sulphonamides, para-aminosalicylic acid (PAS), phenylbutazone, nitrogen mustards and metallic compounds of arsenic, phosphorus and gold. The liability to this toxic action is sometimes due to excessive or too prolonged administration, but more often there seems to be an idiosyncrasy to the toxic agent. The pathological features vary from a mild reaction with minimal fatty changes and no jaundice, to a severe acute reaction with marked necrosis of cells and hæmorrhage leading to death within a few days. If recovery occurs, permanent structural changes to the liver are rare.

Treatment

When the cause is known and can be removed as is the case with dietary deficiency, hepatoxic drugs, chemicals or alcohol, this should obviously be undertaken, and specific antidotes given if these are available.

Liver cells have a remarkable regenerative capacity even when submitted to serious damage from toxic and infective agents. Great improvement in liver function may occur spontaneously or consequent on treatment, even although widespread structural changes persist. Every experienced physician has seen patients with severe ascites or hepatic coma who have made remarkable recoveries which resulted in a return to his or her former occupation. Hence treatment should be vigorous and persistent even although it is largely symptomatic. The course of parenchymal disease of the liver, as is well exemplified by infective (virus) hepatitis, is so unpredictable that it is extremely difficult to assess the value of any therapeutic measures. Treatment will now be discussed under the headings, ‘ Acute Parenchymal Disease of the Liver ’ (acute hepatitis), ‘ Subacute Parenchymal Disease of the Liver ’ (subacute hepatitis) and ‘ Chronic Parenchymal Disease of the Liver ’ (chronic hepatitis ; hepatic cirrhosis).

Acute parenchymal disease of the liver (acute hepatitis)

For amœbic hepatitis and Weil’s disease the administration of emetine and antibiotics respectively is clearly indicated. For hepatitis due to poisoning with heavy metals, *e.g.* arsenic, mercury, copper or gold, chelating agents such as penicillamine or dimercaprol (BAL) are of real value. For hepatitis, the sequel to yellow fever, infective (virus) hepatitis and many hepatoxic agents, no specific treatment is available, but good results can be expected in most cases from the well-tried programme of rest, abstinence from alcohol, and diet.

Rest in bed is essential during the acute stage of both toxic and infective hepatitis and should be continued until the appetite has returned, the liver is no longer tender, the morning urine is free of urobilinogen and the serum bilirubin is less than 1·5 mg./100 ml. *Alcohol* in all forms should be strictly prohibited.

Diet.—There are certain general principles on which to base the dietetic treatment of acute hepatitis which are founded on sound experimental evidence and clinical experience. Thus there is good reason to believe that a high caloric intake is important in accelerating convalescence. Accordingly, every effort should be made to induce the patient to overcome his lack of appetite, nausea and distaste for food by ensuring that meals are well cooked and attractively served. A high carbohydrate intake is essential, not only as a source of calories but because of the proven value of carbohydrates in the prevention and treatment of experimental injury to liver cells. An adequate intake of protein is desirable because of the sound clinical and experimental evidence of the adverse effects of protein malnutrition on hepatitis. However, in severe cases of acute hepatitis and in the terminal stages of chronic hepatitis, a careful watch must be kept for evidence of increasing hepatic failure, including mental confusion and other neurological signs of ammonia intoxication which indicate approaching coma ; and when these are present the protein intake must be severely restricted or even totally forbidden until improvement occurs.

There is no satisfactory evidence to show that the course of the disease is influenced by the fat content of the diet which may be high, moderate or low. It is difficult, however, to construct a high calorie diet in which the fat content is less than 80 to 100 g./day. When jaundice is marked or moderate and nausea and lack of appetite are present, fat and fatty foods may be poorly tolerated. In addition the absorption of fat from the intestine is impaired because of the lack of bile salts. Under these circumstances the intake of fat must be restricted temporarily to 20 to 50 g. daily. Diets Nos. 8 and 9 will be suitable. Fried foods are badly tolerated and the foods rich in fats listed on page 824 should be avoided. When the appetite has returned, milk and butter are usually well tolerated and should be allowed *ad lib* unless the patient finds that they do not agree with him.

Supplements of amino acids and casein hydrolysates by mouth or by infusion are of no therapeutic value, and methionine is potentially dangerous, especially in severely ill patients, as it may induce hepatic coma. Choline is also unnecessary.

The development of œdema and especially ascites are other features which necessitate vigorous dietetic treatment, including great restriction of sodium (p. 570).

Loss of appetite and nausea are prominent features of the early stages of severe acute hepatitis and this may greatly complicate the dietary treatment of the disease. When there is fever and intense distaste for food, it may only be possible to give the patient sweetened fruit drinks and to persuade him to eat small quantities of any food for which he has a fancy. For such severely ill patients, it will generally be found advisable to prescribe for a few days an entirely fluid diet of at least $2\frac{1}{2}$ to 3 *l.* daily, given in small feeds at 2-hourly intervals. To secure a high intake of carbohydrate, orangeade or lemonade sweetened with glucose or lactose should be drunk freely. If possible, 200 to 300 g. of carbohydrate should be taken every 24 hours. In very severe cases it may be necessary to give a 10 to 20 per cent. solution of glucose or fructose intravenously administered through a polythene tube inserted into a large vein ; in which case thiamine (20 mg. daily) should be added to the fluid prior to its infusion. In addition potassium salts should be given orally.

Provided there is no evidence of impending coma or neurological disorders, a limited amount of protein should be allowed. Initially the total intake should not exceed 50 g. daily and this should be given in the form of fresh skimmed milk or skimmed milk reconstituted from dried skimmed milk powder ; one pint of either contains approximately 20 g. of protein. As soon as possible a diet should be given which will cover the immediate needs for protein and calories ; the fat usually has to be severely restricted. Diet No. 8, very low in fat and high in carbohydrate, is suitable for the initial treatment of severe hepato-cellular failure. With further improvement Diet No. 9 should be started. This diet is still low in fat, containing only about 50 g. If it is well tolerated, the fat intake can be increased by adding butter or margarine and substituting whole milk for skimmed milk until the patient is eating a generous diet, high in calories and rich in protein (100 to 130 g.). Diet No. 10 is an example of such a diet, suitable when convalescence is fully established.

Drugs.—In acute and subacute cases of hepatitis not responding to the therapeutic measures discussed above, corticosteroids, *e.g.* prednisone, in large dosage for 3 weeks or longer may produce marked clinical improvement and also a rise in serum albumin.

Subacute parenchymal disease of the liver (subacute hepatitis)

Recovery from the acute phase of an attack of hepatitis is usually rapid but sometimes there may be many weeks or even months before it is complete. The appetite during this stage often remains poor, particularly for fats and fried foods. The patient may be easily fatigued and the liver may remain enlarged and tender.

The same principles for dietary treatment as in acute hepatitis apply : a generous diet high in calories and rich in protein and carbohydrate should be given. It is very important to get the patient to eat. If he has been previously on a low fat diet, the fat intake should be gradually increased. Fried foods are best avoided until convalescence is complete. Well cooked and attractively served foods will do more to restore appetite than too great attention to the chemical composition of the diet. Diet No. 9 will be found satisfactory for the initial treatment of a case of moderate severity. With further recovery Diet No. 10 should be started.

Alcohol tends to bring on attacks of nausea with abdominal discomfort and loss of appetite. For this reason most physicians impose an absolute ban on alcohol during the acute and subacute stage and for 6 months after recovery.

Chronic parenchymal disease of the liver (chronic hepatitis ; hepatic cirrhosis)

In the great majority of patients who have had an attack of hepatitis the liver heals completely in the course of time. In a small minority, probably less than one in a thousand in the case of infective (virus) hepatitis, complete healing does not occur ; a fine fibrosis starts around the portal tract and the subacute stage passes imperceptibly into chronic cirrhosis of the liver. This condition may develop from many causes other than infections of the liver, and in Great Britain it is not uncommon to fail to establish any ætiological factor.

The dietetic treatment of hepatic cirrhosis is much more likely to be successful when the cause lies principally in the previous ingestion of a poor diet, as occurs frequently in underdeveloped countries, and in alcoholics, than when the disorder is the end-result of infective or toxic agents and the patient has been eating well.

When cirrhosis of the liver has advanced to a late stage, there are always associated signs of malnutrition (loss of flesh and a low level of albumin in the plasma), and a disturbance of electrolyte balance (especially sodium retention) ; œdema commonly develops. Obstruction to the hepatic and portal veins leads to congestion of abdominal viscera and ascites.

There is no specific treatment for hepatic cirrhosis secondary to infective or toxic agents. A high calorie, high protein intake, such as Diet No. 10, is desirable. This may be difficult to achieve in the late stages of the disease on account of the poor appetite. The protein intake in the diet can be supplemented by 20 to 40 g. of Casilan (Glaxo) or Lonalac (Mead Johnson) daily, which may be given in milk, soups or ice-cream. These proprietary foods, which consist of 90 per cent. milk protein, are useful when œdema and ascites are present because they are rich in protein and almost salt-free. Vitamin supplements may be required in appropriate doses for specific deficiencies, *e.g.* vitamin K for the bleeding tendency due to hypoprothrombinæmia and also vitamin C and the vitamin B complex. Alcohol should be forbidden or taken only in very small amounts and never by those whose cirrhosis has been due to alcoholism. If the patient can take and digest a high calorie, high protein diet as indicated above, temporary improvement can be anticipated in most cases of cirrhosis of the liver. When the condition is due to alcoholism, provided the damage is not too far advanced, excellent therapeutic results can confidently be expected *provided* the patient is willing to accept strict abstinence. The treatment of the principal complications, namely ascites, portal hypertension, the hypersplenic syndrome and hepatic coma, requires to be considered separately.

Ascites.—The three principal factors responsible are: (1) portal venous hypertension and lymphatic obstruction secondary to intrahepatic fibrosis; (2) reduced osmotic pressure of the plasma due to a failure of the liver to manufacture albumin; (3) increased retention of fluid and sodium. An important cause of œdema and ascites in hepatic failure is excessive renal tubular absorption of sodium consequent on an increased production of the hormone aldosterone by the adrenal gland and the reduced capacity of the damaged liver to inactivate it. Large quantities of aldosterone have been demonstrated in the urine of patients with cirrhosis of the liver and ascites. Another factor which may be concerned in sodium retention in hepatic failure is a lowered renal blood flow, and hence a reduced glomerular filtration rate. The ascitic fluid contains considerable amounts of protein. Paracentesis abdominis, while reducing the unpleasant effects of abdominal distension, has the unfortunate result of reducing the body's stores of protein and hence still further lowering the osmotic pressure of the plasma. The modern treatment of ascites, which is designed to reduce the need for paracentesis to a minimum, consists of giving a diet rich in protein and low in sodium, and the prescription of diuretics to increase the urinary output of sodium and fluid. For this purpose mersalyl is very effective; chlorothiazide has also been used, but is more liable than mersalyl to aggravate or precipitate the neurological features of hepatic failure. The construction of a high protein diet which is also low in sodium presents considerable difficulty because the protein-rich foods (meat, eggs, dairy products) have a high sodium content. Proprietary preparations of milk protein such as Casilan (Glaxo) or Lonalac (Mead Johnson) which are rich in protein and practically free from sodium are of great value for this purpose. If signs of impending hepatic coma are noted, the intake of protein must be drastically reduced. The daily intake of sodium should be reduced by the use of the restricted salt intake regime described in detail on page 570. Drastic reduction of the sodium intake by the use of the low-sodium diet (Diet No. 14) may be required. If the ascites fails to resolve there should be no hesitation in putting the patient temporarily on the minimum sodium diet (Diet No. 15). Fluid need not be restricted.

When the response to the above treatment is poor and when the sodium retention is believed to be due to an excess of aldosterone, spironolactones, which antagonise the action of aldosterone on the distal renal tubular cells, are worthy of trial. They are particularly effective when given together with the diuretic, chlorothiazide, because the spironolactones reduce the absorption of sodium from the distal renal tubules, while the chlorothiazide has a similar effect on the proximal renal tubules. Another advantage of the spironolactones is that they cause a marked reduction in the excretion of potassium in the urine which regularly occurs when the chlorothiazide group of drugs is given.

As a result of these measures the accumulation of ascitic fluid decreases and may finally cease, and the level of serum albumin usually increases. Thereafter the sodium intake can be gradually increased, but it is probably unwise for the patient to add table salt to his food. Salt-rich foods should also be avoided (p. 144).

PORTAL HYPERTENSION.—This frequently leads to the production of varicose veins in the lower end of the œsophagus and in the stomach. From these severe hæmorrhage may arise, which often proves fatal. Portal hypertension may be reduced by natural processes, *e.g.* by the spontaneous development of anastomotic communications between the portal and systemic circulations which enable the portal venous blood to short-circuit the intrahepatic or extrahepatic block. A variety of surgical operations have been devised, which produce shunts between the two venous systems. Such operations are technically difficult and should only be undertaken by experts who clearly understand both the risks to the individual and the indications. Shunt operations should only be performed if the risk to life from hæmorrhage is greater than the risk to life from hepatic failure. The dietetic treatment of portal hypertension is that of the underlying disorder of the liver as already described. Prior to and for some days after undertaking a ‘ shunt ’ operation on a patient with evidence of hepato-cellular failure, the protein intake should be severely restricted because of the danger that hæmorrhage and post-operative shock may induce acute hepatic failure with coma (see below). Iron should be given for the hypochromic anæmia which results from hæmorrhage from the œsophageal and gastric varices, and repeated blood transfusions may be required when the amount of blood lost is large.

HEPATIC COMA.—This may develop in acute or subacute hepato-cellular failure or more frequently as a terminal feature of chronic hepatitis (cirrhosis of the liver). It is a grave emergency which is usually resolved in a few days either by death or by recovery. The provision of adequate nutrition during this emergency may be very difficult because there is usually a marked loss of appetite, and nausea and vomiting readily occur. It is now widely agreed that proteins and amino acids aggravate severe liver failure. The principle underlying the modern treatment of hepatic coma is the assumption that the altered cerebral metabolism leading to coma is due to the toxic effects of nitrogenous end-products absorbed from the alimentary tract. In hepatic coma the level of blood ammonia is usually two to five times higher than the normal figure of about 1 μg./ml. The basis of treatment with glutamic acid was the belief that this substance would combine with ammonia to form the innocuous substance, glutamin. This form of treatment has not been found to be satisfactory.

For energy needs (about 1600 Cal./day) it will be necessary to rely on carbohydrates. It is important to avoid starvation as this involves drawing upon reserves of body fat and proteins, which may not be adequately metabolised by the damaged liver. It is also necessary to provide ample fluids and to preserve electrolyte balance which may be gravely upset, especially if vomiting is severe.

Treatment consists of sterilising the gut temporarily with oral chlortetracycline, or preferably neomycin, and of stopping all dietary protein and giving 1600 Calories daily in the form of glucose or lactose drinks flavoured with fruit juice by mouth in small feeds at 1-hour or 2-hour intervals. If the condition of the patient is so grave that he can neither ingest nor retain sufficient fluid or sugar, oral treatment must be replaced or supplemented by intragastric tube feeding or by the infusion of a 10 to 20 per cent. solution of glucose or fructose through a polythene tube inserted into the inferior or superior vena cava. At least 2 *l.* of fluid should be given daily. Supplements of potassium and of sodium, especially if there is vomiting, will be needed. The daily determination of the electrolyte balance greatly facilitates assessment of dosage. Thiamine (10 mg./day) should also be added to the infusion fluid, and vitamin K and a preparation of the B complex given parenterally during the acute stage.

In patients with severe hepatic failure there is a danger of inducing coma if ammonium salts, ammonium exchange resins or methionine in large dosage is given. For the same reasons the sedatives, morphine or the barbiturates are contraindicated. Shock and hypotension, the results of hæmorrhage, accident or operation, are potent causes of precipitating hepatic failure and coma, and should be energetically treated.

As soon as signs of recovery from hepatic failure are noted, *e.g.* a reduction in the degree of mental confusion or apathy, increments of 20 g. of protein should be added to the diet every 2 or 3 days until a normal or high intake of protein has been reached. A pint (0·5 *l.*) of skimmed milk contains approximately 20 g. of protein and this can be given in small feeds several times a day as a supplement to the glucose drinks. The consumption of skimmed milk can be gradually increased until 3 pints (1·5 *l.*) are taken daily. This will provide about 60 g. of protein. If the patient's condition is still improving, solid foods such as lean meat, fish, bread, jam and fruits can be added to the diet until the patient is taking the generous high calorie, high protein diet (No. 10). This regime is frequently successful in the treatment of hepatic coma following an acute attack of hepatitis. The results are not nearly so good when hepatic failure develops as a terminal event in chronic hepatitis. In such cases it is usually necessary to keep the patient indefinitely on a reduced protein intake (40 to 50 g.), otherwise mental symptoms tend to recur.

OBSTRUCTIVE JAUNDICE

It is necessary to distinguish jaundice due to obstruction of the main bile passages by stone, stricture or malignant disease, from the jaundice occurring in acute hepatitis resulting from cellular damage and intra-hepatic obstruction. In the former, the liver cells are, at least for some time, relatively uninjured and hence if the obstruction is removed in time, no permanent cellular damage will occur. Nevertheless, it is advisable to ensure that the patient takes an ample supply of carbohydrate and protein of good quality in the form of skimmed milk and skimmed milk powder. This is particularly desirable as a pre-operative measure to prevent the toxic effects of general anæsthesia. Since the flow of bile is reduced, a low intake of fat is indicated. Treatment therefore consists of (1) the relief of the obstruction, either by medical treatment (heat to the abdomen, sedative and antispasmodic drugs) or by surgical intervention; and (2) the prescription of a suitable diet. When the obstruction is suddenly produced, as by impaction of a gall-stone, colic, vomiting and fever may be the presenting symptoms, which necessitate a fluid diet on the lines suggested for acute cholecystitis (p. 541). When the acute symptoms subside, or if the obstructive jaundice develops slowly as the result of a stricture or of pressure on the common bile duct, a diet containing about 400 g. of carbohydrate, 80 g. of protein and 20 g. of fat will be found suitable. Diet No. 8 will meet these requirements. With improvement in appetite and reduction in the jaundice, the daily intake of fat should be increased first to 50 g. (Diet No. 9) and later to 100 g. (Diet No. 10).

If jaundice continues for more than a few days supplements of the fat-soluble vitamins A, D and K should be given parenterally. In long-continued obstructive jaundice there is a real risk of osteomalacia developing; accordingly, the calcium content of the diet should be augmented by the oral administration of calcium gluconate. If the obstructive jaundice cannot be relieved and continues for many months or years, the condition will terminate in hepatocellular failure, the treatment of which is described on page 536.

DISEASES OF THE GALL-BLADDER AND BILE DUCTS

Anatomy and physiology

About 1 *l.* of bile is secreted by the liver every 24 hours. Most of the bile enters the gall-bladder through the cystic duct, entry into the duodenum being prevented because the sphincter of Oddi is closed. During its stay in the gall-bladder, the bile is concentrated five to ten times. The principal function of the gall-bladder is to act as a reservoir for bile and to discharge it into the bowel when it is most needed, namely after meals. After the ingestion of food the sphincter of Oddi periodically relaxes, the gall-bladder contracts and its contents are expelled through the cystic duct into the common bile duct and thus into the duodenum. The stimulus for this activity is the entry of food into the small intestine ; this causes the mucosa of the duodenum and jejunum to secrete a hormone, cholecystokinin, which is carried in the blood to the gall-bladder and causes it to contract. Fats and foods rich in fats are especially effective for this purpose. The gall-bladder and the sphincter of Oddi appear to be reciprocally innervated. Thus vagal stimulation causes contraction of the gall-bladder and relaxation of the sphincter, while stimulation of the sympathetic nerves produces the reverse effects. Many physicians believe that disturbance of these reciprocal effects and of the hormonal mechanism may be responsible for initiating both organic disease and functional disorders of the biliary tract. The latter include biliary achalasia (failure in relaxation of the sphincter of Oddi), biliary dyskinesia (spasm of the sphincter of Oddi) and bilious vomiting associated with such conditions as migraine.

Acute Cholecystitis

Gall-stones are present in 90 per cent. of gall-bladders, the seat of acute cholecystitis.

The treatment of acute cholecystitis is, at the onset, essentially that of any acute febrile illness. The patient must be kept at rest in bed. Pain must be relieved with pethidine and atropine. If this is not successful morphine will be required. Heat should be applied to the gall-bladder region and large quantities of fluids should be drunk. So long as the gall-bladder is acutely inflamed, it is advisable to keep the organ as far as possible at rest. To this end fat, which causes contraction of the gall-bladder, should be excluded from the diet, and the intake of protein, which has a similar but less marked effect, should be reduced to 30 to 40 g. For such severe cases it is advisable to prescribe for a few days an entirely fluid diet of at least 2 to 3 *l.* daily, given in small feeds at hourly or 2-hourly intervals. Two hundred to 300 g. of carbohydrate should be taken every 24 hours in the form of orangeade or lemonade sweetened with glucose or lactose ; the protein intake of 30 to 40 g. is obtained from fresh skimmed milk or skimmed milk reconstituted from dried skimmed milk powder, of which 1 pint of either contains approximately 20 g. of protein. Fruits, stewed and sieved, and fruit juice may be allowed if desired by the patient. Sulphadimidine or tetracycline should be given daily by mouth, or penicillin and streptomycin by injection, since these drugs have been shown to reach the wall of the gall-bladder and also to be present in the bile in high concentration. Drugs to increase the flow of bile and stimulate the gall-bladder to contract are strongly contra-indicated in the acute stage.

When the condition settles down, as it usually does within 2 or 3 days, clear soups, beef tea, milk, fruit jellies, and cereals may be added, and the diet is rapidly built up to normal or to that recommended for chronic cholecystitis (see below). If fever, abdominal tenderness and colic continue unabated for more than 2 or 3 days, gangrene of the gall-bladder may have occurred, and surgical help should be sought at once.

CHOLELITHIASIS AND CHRONIC CHOLECYSTITIS

Under certain abnormal conditions the bile loses its capacity for retaining cholesterol in solution, which is then precipitated as a viscous deposit or crystallises out with the formation of calculi. Any factor leading to a disturbance of the equilibrium existing between the various components of bile may lead to this result. Such factors include bacterial and chemical inflammation of the gall-bladder, stasis or slowing of excretion of bile, advancing age, insufficient exercise, pregnancy, changes in the *p*H of the bile and reduction in the ratio of bile acids to cholesterol. It is not surprising, therefore, that gall-stones are frequently found *post mortem* in people dying from a wide variety of causes. It has been stated that about 10 per cent. of all adults in the U.S.A. have or will have gall-stones.

The treatment of cholelithiasis with accompanying cholecystitis is primarily the province of the surgeon. Osler is credited with the statement that " the medicinal treatment of gall-stones is a chapter in our book of therapeutics, the leaves of which are best turned very rapidly." Nevertheless, the physician has an important part to play in deciding on the most suitable time for operation and in carrying out pre-operative treatment on the lines described below. In addition, the physician must assume responsibility for the treatment of biliary dyskinesia, non-calculous cholecystitis and calculous cholecystitis should such develop in a patient unsuitable for operation because of advanced cardiac or renal disease.

The principles of treatment can be summarised as follows :—

1. **Reduction of weight.**—As the majority of these patients are overweight, the prescription of a reducing diet is of fundamental importance (Diet No. 1).

2. **Improvement of drainage of the biliary tract.**—This is needed since stasis is recognised as an important factor in causing and prolonging infections and producing gall-stones. The following may be helpful : (*a*) the prescription of special deep breathing and abdominal exercises, and regular exercise in the fresh air ; (*b*) the use of drugs which stimulate the flow of bile or alter its physico-chemical composition (*e.g.* bile salts), or cause contraction of the gall-bladder, or reduce spasm in the bile ducts or at the sphincter of Oddi (*e.g.* magnesium sulphate, the nitrites, belladonna and olive oil). Sulphonamides or antibiotics should also be given, for these improve drainage by controlling infection with its consequent catarrh.

3. Dietetic measures

FAT CONTENT OF THE DIET.—It is both unnecessary and unwise to limit too strictly the fat content of the diet in chronic cholecystitis. The passage of fat into the small intestine is recognised to be not only the physiological but also the most effective means of causing contraction of the gall-bladder and ducts, and thus inducing drainage of the biliary tract. In addition the exclusion of butter, margarine, milk and cream in a chronic disease makes the diet unpalatable and monotonous and low in its content of fat-soluble vitamins. Many textbooks have recommended a severe restriction of fat on the grounds that fatty foods are rich in cholesterol, which is an important constituent of gall-stones. We disagree with this viewpoint for the reasons stated below. Some restriction of fat, however, is essential if obesity is present or if the patient finds fatty foods cause nausea or indigestion. Natural fatty foods, such as milk and butter, in moderate quantities are in our experience well tolerated, and we allow our patients from 20 to 40 g. of butter or margarine (see below) and $\frac{1}{2}$ to 1 pint (0·25 to 0·5 *l.*) of milk in the 24 hours, due regard being given to whether obesity is or is not present. Beef and mutton are allowed provided excess of visible fat is removed, as also are white fish, rabbit and chicken ; but the fatty meats (duck, goose and pork), the fatty fish (salmon and herring) and fried foods should be avoided because of their tendency to cause indigestion and obesity which are so often present in sufferers from chronic gall-bladder disease.

CHOLESTEROL CONTENT OF THE DIET.—Many doctors have recommended that foods rich in cholesterol should be excluded from the diet of patients suffering from cholelithiasis or cholecystitis. This advice requires modification for the following reasons :—

(*a*) A normal diet may contain approximately 0·5 to 1 g. of cholesterol daily, but endogenous production exceeds this amount by two to five times.

(*b*) The evidence that the incidence of gall-bladder disease in patients suffering from disorders characterised by a high plasma cholesterol (*e.g.* diabetes mellitus, myxœdema, nephrosis) is greater than in persons with a normal level of plasma cholesterol, is far from satisfactory, provided that the factors of age and obesity are comparable in the two groups.

(*c*) Investigations carried out under the direction of one of us (Davidson, 1944) showed that there was no necessary correlation between the intake of cholesterol in the food and the level of cholesterol in the plasma or bile. Similar values were obtained whether the patients ingested 300 or 2000 mg. of cholesterol daily.

(*d*) Cholesterol feeding experiments in animals are not necessarily applicable to man. When large amounts of cholesterol are fed to some animals (rats, guinea-pigs, rabbits) the level of cholesterol in the plasma is raised and the cholesterol and fat content of the liver is markedly increased. Cook (1942) pointed out that if the amount of cholesterol given in these experiments in animals is translated into terms of cholesterol intake from some common foodstuff for man, then a man of 65 kg. weight would have to take 270 eggs a day to equal the amount given to the rat, or 54 eggs a day to equal that given to the rabbit. It is obvious, therefore, that it is quite unjustifiable to advocate low-fat, low-cholesterol diets in the treatment of diseases of the biliary tract in man on the basis of such animal experiments.

The severe restriction of fatty foods with the object of preventing the formation of gall-stones rests on no sound basis. It seems most unwise to withhold from the patient the beneficial effects which result from the ingestion of fat, because of unproven hypotheses as to the metabolism of cholesterol. It is not generally realised that there exists no correlation between the cholesterol and fat content of different foods and yet this is clearly shown in Table 39, 1.

TABLE 39, 1. *The cholesterol content of some foods compared with their fat content*

	Cholesterol (mg./100 g.)	Fat (mg./100 g.)	Ratio (fat/cholesterol)
Rich sources—			
Sweetbreads . . .	2500	15,000	6 : 1
Brains	2000	15,000	7 : 1
Fish roes . . .	300	2,000	7 : 1
Eggs (two without shell) .	600	10,000	16 : 1
Medium sources—			
Kidneys . . .	300	7,500	25 : 1
Liver	150	7,500	50 : 1
Butter	250	80,000	320 : 1
Low sources—			
Meat, lean . . .	65	13,000	200 : 1
Milk	10	3,600	360 : 1
Poor sources—			
Cereal, bread, fruits and vegetables . . .	Less than 10	Less than 2,000	...

From Table 39, 1, it may be concluded that sweetbread, brains, fish roes, kidney and liver should be excluded from the diet since their relatively low fat content, as compared with that of butter, cream or cheese, will be of little value in promoting biliary drainage, while their high cholesterol content may possibly be a disadvantage. Vegetables and cereals contain small amounts of sterol, principally as phytosterol which is not assimilable. Restriction of these foods will obviously not affect cholesterol metabolism. If it were desired to limit the cholesterol content of the diet to a minimum and at the same time provide the physiological stimulus for gall-bladder contraction, it would be rational to replace butter by olive oil or by margarine made from vegetable oil. A diet containing 1 pint (0·5 *l.*) of milk, 2 oz. (60 g.) of butter, and an average helping of fish or meat at two meals in the day will yield about 300 to 400 mg. of cholesterol. Cook's monograph (1958) should be referred to for an excellent review of cholesterol metabolism and for further information on the sterol contents of tissues and foods.

Eggs and fried foods.—It is a well-recognised clinical observation that many patients suffering from diseases of the liver, gall-bladder and biliary tract are unable to eat fried foods and eggs because of the consequent flatulent dyspepsia. It is easy to understand why they are unable to tolerate excess of fat or fried foods, but the reason for the particular intolerance to eggs is far from clear. In our experience the idiosyncrasy in some cases is associated especially with the ingestion of *fried* eggs, and no symptoms may be caused by lightly boiled or poached eggs or eggs present in custard or sponge cake. We have frequently allowed our patients with chronic disease of the gall-bladder to take one or two eggs a day if they so desired, and we have never been satisfied that the clinical course of the disease was adversely affected in any way.

The fat intake should vary from 40 to 70 g. and the carbohydrate from 100 to 400 g. daily, depending on whether obesity is or is not present. Diet No. 11 is suitable or Diet No. 1 if the patient is obese.

Other dietetic measures.—The protein content of the diet should be at least 80 g. per day, as protein has been shown to be an effective stimulator of gall-bladder contraction, and to play an important part in maintaining the function of the liver. Lean beef and mutton, chicken and white fish are allowed in moderate quantity.

The greatest care should be taken to avoid large meals and indigestible articles of food (p. 824) because of the ease with which dyspepsia occurs in patients suffering from chronic disease of the gall-bladder.

Lastly, but not least in importance, is the need for ample quantities of fluids, which should be taken first thing in the morning and last thing at night, and between meals when the stomach is empty.

4. **Symptomatic treatment**

Dyspepsia, flatulence and constipation are features which commonly accompany chronic cholecystitis and which will require treatment.

FUNCTIONAL DISORDERS OF THE GALL-BLADDER AND BILIARY TRACT (BILIARY DYSKINESIA)

Biliary dyskinesia has been defined as an obstruction to the flow of bile into the duodenum due to a neuromuscular disturbance of the sphincter of Oddi ; as a result symptoms suggestive of organic disease of the gall-bladder are present. The existence of biliary dyskinesia is disputed by many authorities.

Treatment.—Treatment consists of the use of sedative and antispasmodic drugs, the relief of any underlying anxiety state and observance of the dietetic principles described for chronic calculous cholecystitis (p. 542).

CHOLANGITIS, CHOLANGIO-HEPATITIS AND BILIARY CIRRHOSIS

An ascending infection of the small bile duct is liable to arise if partial or complete obstruction to the flow of bile develops. The most important causes of obstruction are gall-stones, a fibrous stricture of the common bile duct, a tumour of the bile ducts or a carcinoma at the head of the pancreas. Fever, leucocytosis and intermittent jaundice are the main presenting features of cholangitis. If the infection cannot be controlled, cholangio-hepatitis will result and eventually the patient will die of chronic intrahepatic obstructive jaundice (biliary cirrhosis) and progressive hepatic failure. Treatment consists of (1) surgical removal of the obstruction when this is possible, to be followed by drainage of the common bile ducts, (2) the administration of antibiotics, *e.g.* penicillin and streptomycin or a wide-spectrum antibiotic such as tetracycline, and (3) dietetic treatment for cholangio-hepatitis according to its severity and the stage of development of its sequelæ—biliary cirrhosis and hepatic failure—on the lines described for acute, subacute and chronic hepatitis.

CHAPTER 40

DISEASES OF THE CARDIOVASCULAR SYSTEM

ALL the organs of the body depend for their nutrition on an adequate supply of blood. This is pumped to them by the heart through the arteries. As age advances degenerative changes occur in the organs, which can be attributed to a reduced blood supply consequent upon arterial disease rather than to the effect of an ageing process arising within the cells themselves.

The great increase in recent years in the incidence of ischæmic heart disease, a sequel of atherosclerosis, is a matter of concern to doctors, research workers and laymen. There must be few persons who have reached middle age who have not lost a friend or relative, at the height of his career and with his family responsibilities at a maximum, as a result of disease of the coronary arteries. This subject is widely discussed by writers in the press and by commentators on the radio and television circuits. It is not surprising therefore that the laity should seek reliable information from the family doctor on such an important matter, and it is desirable that he should be able to give his patients sound information on the causes of atherosclerosis and ischæmic heart disease, and also sensible advice on prevention and treatment. To help the doctor in this task the complex problem is reviewed below in some detail.

DEGENERATIVE ARTERIAL DISEASE

There are three main types of degenerative disease of the arteries :

1. Atherosclerosis (atheroma)*
2. Arteriosclerosis.
3. Medial sclerosis (Monckeberg's sclerosis).

Atherosclerosis is primarily a disease of the intimal lining of the vessels and arteriosclerosis of the elastic and muscular medial coat. Pathologically they are two quite distinct processes, but as both are extremely common in middle and old age this is often overlooked. Before considering these diseases, the structure of the arterial walls is briefly described.

The structure of the arterial wall.—This consists of three layers :

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* Prior to the publication by the World Health Organization (1958) on the Classification of Atherosclerotic Lesions, it was customary to describe these lesions as 'atheroma' in Great Britain and as 'atherosclerosis' in the U.S.A. The WHO Committee recommend that the name 'atherosclerosis' should be used. As uniformity in nomenclature throughout the world is obviously desirable, we accepted this decision.

(1) An inner *tunica intima* composed of a thin layer of endothelial cells and beneath these a few elastic fibres lying in an amorphous intercellular substance. (2) A middle *tunica media* composed of elastic, muscular and fibrous tissue. In the large arteries, elastic tissue allows the vessel to be dilated by the force of each beat of the heart and to recoil in diastole. In this way the elasticity of the arteries evens out the flow of blood to the tissues. In the small arteries (the arterioles), the *media* is composed mainly of muscle ; this muscle can alter the calibre of the vessel and so directs the flow of blood to different parts of the body. (3) An outer *tunica adventitia* composed of loose connective tissue. In this, run the small blood vessels and nerves that supply the media.

ATHEROSCLEROSIS

Atherosclerosis is a pathological condition which can only be diagnosed accurately *post mortem.* Nevertheless, since ischæmic heart disease can be diagnosed clinically with reasonable certainty and is so closely related to atherosclerosis, it is legitimate to use clinical records of this disease, obtained from death certificates, hospital records or special surveys as an index of the incidence of atherosclerosis. Much more is known about the incidence of atherosclerosis in the coronary vessels than in the other arteries. For this reason the chemical pathology, epidemiology, prevention and treatment of atherosclerosis and its sequel, ischæmic heart disease, are discussed concurrently.

Although often associated with and accelerated by hypertension, atherosclerosis may be advanced even in the presence of a normal blood pressure. It may also occur in response to a local rise of pressure, as is found in the pulmonary arteries of patients with pulmonary hypertension. The pulmonary artery is not otherwise subject to atherosclerosis.

Pathology

Description.—Atherosclerosis is first seen as fatty streaks or spots (Stage I). These are thickenings of the intima which appear as slightly raised flattened yellow streaks, usually running longitudinally along the vessel. Under the microscope it can be seen that the elevation is caused by a new formation of connective tissue cells within the intima and many of these cells are distended with droplets of fat and contain much cholesterol. Next a fibrous plaque (Stage II) develops between the *intima* and the *media*. These are circumscribed, elevated intimal thickenings, which are firm and grey or pearly white. They vary in size from one up to several millimetres in diameter and are irregular in shape. Large plaques project into the lumen sufficiently far to block or slow down the flow of blood in an artery of medium size. At first the media under the plaque is usually normal. When the plaques contain large amounts of fatty material they become soft (Stage III). Finally the surface of the plaque breaks down and an atheromatous ulcer with ragged irregular edges develops (Stage IV). Fibrous tissue formed at the base of such an ulcer leads to scarring which may narrow and distort the shape of the vessel. Calcium salts may be deposited in the base of the ulcer and hæmorrhages may occur. Thrombosis may result partly from the above pathological changes in the vessel wall and partly from alteration in the clotting mechanism (p. 551). The four stages described above are based on a classification by the World Health Organization (1958).

Mode of formation.—Atherosclerosis probably arises in two ways (Duguid, 1954 ; Morgan, 1956 ; Duguid and Robertson, 1957). First a microscopic clot may form in the circulating blood and may stick to the vessel wall. The fibrin in this clot becomes ' organised ' on the surface of the intima. Connective tissue cells enter the clot, fibrous tissue is formed and fat deposited in and around these cells. At the same time endothelial cells overgrow the clot and re-establish the continuity of the intima lining of the vessel. The remains of the clot, together with a mass of fatty material and some connective tissue, form the plaque.

An alternative method for the formation of the plaque is from *subintimal* hæmorrhages. The arteries are elastic tubes which dilate and recoil at each beat of the heart. If there is any loss of elasticity of part of the wall, as by fibrous thickening, this may set up mechanical stresses leading to structural disorganisation. Small hæmorrhages, usually just beneath the *intima*, may result. Cholesterol and other lipids are then deposited at the site of the hæmorrhage and so give rise to atherosclerosis.

The human species is peculiarly susceptible to atherosclerosis—much more so than is any other animal. If a careful search is made, small streaks of atherosclerosis can be found in the blood vessels of boys and girls even at the age of eight (Geiringer, 1950). By the time middle age is reached, the arteries of most people at post-mortem show Stage I and Stage II atherosclerosis. This does not necessarily interfere with blood flow or cause clinical symptoms.

Effects of atherosclerosis.—During life atherosclerosis may be recognised by its effects on the body, but it should be remembered that the absence of clinical features does not exclude its presence, and it develops in persons of all ages but not necessarily to an extent to affect health. When narrowing of a vessel occurs, serious impairment of the blood supply to important structures may result. Atherosclerosis in the coronary arteries, for example, is responsible for angina pectoris, and in the cerebral arteries for many mental changes in old age ; in the vessels of the legs it may be responsible for intermittent claudication. Complete obstruction to blood flow, usually due to thrombosis, results in cardiac infarction, hemiplegia or senile gangrene. Atherosclerosis may exist for a long time without giving rise to intravascular thrombosis, although a damaged arterial *intima* certainly predisposes to clot formation.

Chemical pathology.—That atherosclerotic lesions contain large amounts of fatty material, a big proportion of which is cholesterol, has been known since the time of Virchow, over a hundred years ago. Renewed interest in the lipids present in atherosclerotic lesions arose when it became established that the disorder was associated with a disturbance of the transport mechanism for lipids in the blood. The average levels of plasma cholesterol are higher in patients with atherosclerosis and ischæmic heart disease than in healthy controls. This has been shown in clinics in the U.S.A. (Gertler *et al.*, 1950), in Great Britain (Oliver & Boyd, 1953*b*), in Scandinavia (Biörck *et al.*, 1957) and in many other places. However, a minority of patients with ischæmic heart disease have a normal level of plasma cholesterol and many persons with a high level may remain clinically well for years.

The cholesterol level is only one of several lipid components of the plasma which are raised in ischæmic heart disease. The triglyceride level (Albrink & Man, 1959) and the beta lipoprotein level are also raised (Gofman, 1959). It has also been reported (Kayahan, 1960) that serum globulins from patients with atherosclerosis are able to bind more lipids than serum globulins from healthy persons. There are thus many disturbances of plasma lipids associated with the presence of atherosclerosis, of which the raised cholesterol level is the one most easily measured, but not necessarily the most important.

Recently there have been several studies of the nature of the lipids present in atherosclerotic lesions as compared with those in the plasma. The total amount of lipid in an atherosclerotic lesion may be eight times as much as that in a portion of healthy arterial intima of the same size (Adams, 1959 ; Smith, 1960). Most of the increase is in cholesterol and in triglycerides. The phospholipids are also increased, but often to a lesser extent, so that the phospholipid/cholesterol ratio may be lower in an atheromatous plaque than in healthy intima. It is of interest to note that about 40 per cent. of the total lipids present in the intima of both healthy and atherosclerotic arteries is cholesterol, most of which is esterified with fatty acids. With increasing severity of atherosclerosis, the proportion of cholesterol esterified with polyunsaturated fatty acids increases (Wright *et al.*, 1959 ; Böttcher *et al.*, 1960). These acids, as described in Chapter 6, are known as essential fatty acids. This finding of a high content of essential fatty acids in the cholesterol esters present in atherosclerotic plaques, if substantiated, is difficult to reconcile with the hypothesis (p. 111) that a relative deficiency of these acids is an important contributory cause of atherosclerosis.

The lipids in atherosclerotic plaques resemble at least qualitatively the lipids in the plasma. This suggests the possibility that they have passed through the endothelial lining of the affected vessel to enter the plaque from the circulating blood. As Florey (1960) has pointed out in a valuable discussion of possible mechanisms of the development of atherosclerosis, all too little is known about how substances pass through endothelium. The lipids in the blood are all bound in combination with protein. Hence it is possible that some abnormality of the carrier protein is responsible for facilitating the passage of lipids through the endothelial lining of arteries.

The chemical pathology of the factors which influence thrombosis will now be discussed.

Thrombosis and fibrinolysis.—In atherosclerosis, not only the state of the vessel walls but also the factors which influence the clotting of blood are of importance.

The coagulation of blood has been much studied in test tubes. However, the clot that forms in a test tube differs from a thrombus that forms in a living vessel. A thrombus grows slowly as the blood corpuscles are progressively entrapped and fibrin is formed. As a result a thrombus has a well-defined structure.

Recently there has been great interest in the fibrinolytic system in the blood which can dissolve fibrin and hence is capable of resolving a small thrombus. The growth of a thrombus within a vessel may be the result of a failure of the fibrinolytic system. Astrup (1956) has published an important paper discussing the biological significance of fibrinolysis.

It is now well established that the rate of clotting of blood and the fibrinolytic activity of plasma, when measured in a test tube, is affected by the previous diet of the subject from whom the blood was drawn. A fatty meal, eaten a few hours before the blood is taken, accelerates clotting (Fullerton *et al.*, 1953) and inhibits fibrinolysis (Greig & Runde, 1957). These results have been substantiated and extended by many workers, notably in Great Britain by O'Brien (1958), by Fearnley (1961) and by Maclagan and his group at the Westminster Hospital (James *et al.*, 1961). As regards the nature of the fats responsible for these effects, there is no doubt that dairy fats and eggs accelerate clotting and inhibit fibrinolysis ; unsaturated fats in marine and vegetable oils tend to have the opposite effect, but they have not been extensively studied and published results are conflicting. Other dietary factors may be important. Thus, out of 14 people who drank one pint of beer, 10 showed reduced fibrinolytic activity in the blood two hours later (Fearnley *et al.*, 1960). In 6 of these subjects fibrinolytic activity was unchanged by a large glass of whisky. Moderate exercise has been reported to increase fibrinolytic activity (Ogston & Fullerton, 1961). There is no direct evidence that any of these findings are related to thrombus formation in life. However, the blood of patients with ischæmic heart disease has been reported to clot in certain tests more readily than that of healthy controls (McDonald & Edgill, 1957; James *et al.*, 1961). Fibrinolytic activity has been reported to be high in Africans, in whom it is well known that pathological thrombosis rarely occurs (Franz *et al.*, 1961).

The development of atherosclerosis and the formation of a thrombus in a vessel in life are obviously two different processes with two different causes. However, there may be contributory factors common to both. For example, the state of the blood lipids, as determined by the diet, may influence both processes. Speculation on these subjects is leading to much laboratory investigation of fibrinolysis and clotting. The information collected in recent years has made the problem more complicated and there is much data in the journals which is in need of interpretation. The reader will find useful discussions in papers by Florey (1960) and Oliver (1960).

EPIDEMIOLOGY

Any doctor who has been in practice for more than 20 years will have seen a remarkable increase in the sequelæ of atherosclerosis. Thirty years ago ischæmic heart disease was essentially a disease of men belonging to the well-to-do classes—successful business men and members of the professions. It was uncommon to find a woman affected. Since then there has been a steady increase affecting all classes, but especially in wage earners, in men under the age of 45 and in women over the age of 55.

TABLE 40, 1. *Mortality from ischæmic heart disease*, 1957-58. *Rates per* 100,000 *population of each sex and of the corresponding age group* (*WHO*, 1962*b*)

	Age 45–49		Age 65–69	
	Male	Female	Male	Female
South Africa: Europeans	297	92	1513	707
United States: Whites	251	44	1797	813
United States: non-Whites	247	152	1731	1172
Finland	220	34	1431	660
Canada	214	46	1501	709
Scotland	189	44	1629	817
Australia	174	44	1476	654
England and Wales	131	24	1242	553
Germany: Federal Republic	100	35	886	467
Denmark	97	20	1004	498
Italy	80	31	759	522
Sweden	69	16	979	521
France	38	8	329	141
Japan	44	35	323	227

There is no reason to suppose that atherosclerosis is not also affecting in increasing amounts other vessels, especially in the brain and in the legs; yet there are no reports of increases in cerebral or peripheral arterial disease *comparable* to the increase in coronary artery disease.

Table 40, 1 shows the mortality rates for ischæmic heart disease in middle-aged men and women in many countries. White South Africa, the United States, Finland and Canada head the list. *These are prosperous countries.* In the United States the disease is responsible for 40 per cent. of the deaths in men aged 45 to 64 years. There is no doubt that atherosclerosis and its sequelæ are closely associated with prosperity.

There are few figures available for countries in Asia and Africa, but it is certain that in those in which there is still much poverty the incidence is low, even less than that recorded for Japan in Table 40, 1. Post-mortem examination of the hearts of American and Korean soldiers of the same age group showed a much higher incidence of atherosclerosis in the American hearts. Korean soldiers also had a low level of plasma cholesterol and a low intake of dietary fat in comparison with American soldiers. In South Africa there is a low incidence of ischæmic heart disease in the Bantu in marked contrast to the high incidence in the prosperous white community (Bronte-Stewart *et al.*, 1955). The Cape coloured community is intermediate between the Bantu and the whites, both in their economic status and liability to atherosclerosis. Plasma cholesterol and intake of dietary fat also increase from low levels in the Bantu to high levels in the whites, with the Cape coloured intermediary. There are also several reports from Israel (Brunner & Manelis, 1960 ; Toor *et al.*, 1960 ; Cohen *et al.*, 1961) which relate the incidence of ischæmic heart disease in the Jews to their countries of origin. Incidence is very much lower in poor immigrants from Asiatic countries such as the Yemen, as compared with European immigrants. Katz *et al.* (1959) give many references which show the low incidence of atherosclerosis in Ceylon, Costa Rica, East Africa, Guatemala, India, Indonesia, Iraq, Malaya, Mexico, Nigeria, Okinawa and Uganda.

There is no evidence that Asiatics and Africans possess any racial immunity to the disease. Prosperous Asiatics and Africans who adopt American or European ways of life are frequently affected. The incidence of ischæmic heart disease in Japanese who live in California is ten times that of those who live in Japan (Keys *et al.*, 1957).

There are many differences in the mode of life of those who live in prosperous countries and in those who live in underdeveloped areas of the world. Factors associated with prosperity, which may be responsible for increased atherosclerosis will now be discussed.

POSSIBLE ÆTIOLOGICAL FACTORS

Diet.—In prosperous countries the dietary intake of fat is high and a considerable proportion is of animal origin containing large amounts of saturated fatty acids.

Attempts have been made, notably by Keys (1953) to correlate the death rates from ischæmic heart disease with the total fat in the diet, as reported by FAO from national food statistics. It is certainly true that by selecting suitable countries it is possible to draw graphs demonstrating a correlation between the incidence of ischæmic heart disease and the intake of dietary fat. But it has been shown that equally good correlations exist between these death rates and other dietary factors such as the intake of animal protein (Yerushalmy & Hilleboe, 1957) and even with other signs of prosperity such as the number of radio licences (Yudkin, 1957).

More convincing evidence in favour of the role of dietary fat in the ætiology of atherosclerosis and its sequelæ is the close association between ischæmic heart disease and a high plasma cholesterol level (p. 550) and the undisputed fact that the plasma cholesterol level is determined largely by the quality and quantity of dietary fat (Chapter 6). The sequence :—

$$\text{High intake of saturated fats} \xrightarrow{A} \text{raised plasma cholesterol} \xrightarrow{B}$$

$$\text{atherosclerosis} \xrightarrow{C} \text{ischæmic heart disease}$$

is sensible and there is certainly no chemical or pathological evidence to refute it. While there is first-class experimental evidence to support Stage A (Chapter 6) and few would dispute the importance of Stage C, only circumstantial evidence, as described already in this chapter, is available to justify Stage B. It has not yet been shown that lowering the plasma cholesterol in a group of healthy men reduces the incidence of ischæmic heart disease, or alters the course of the disease once it has been established. Clinical surveys designed to provide this evidence are extremely difficult to organise (p. 559). However, until such evidence is available, there will always remain the doubt that the association between high plasma cholesterol levels and ischæmic heart disease is incidental and not causal.

Another difficulty in accepting the ætiological role of fats in atherosclerosis is that it has not been possible to demonstrate in a homogeneous group of men, that those who develop ischæmic heart disease eat more fat or have dietary habits in any way different from those who do not develop the disease. This objection should not be pressed too strongly, because it is very difficult to collect such evidence, since atherosclerosis develops slowly over a long period.

While it must be admitted that the case against fats has not been proved, we should be surprised if future research fails to show that either the quantity or quality of the dietary fats plays some significant role in the causation of atherosclerosis and its sequel, ischæmic heart disease. Nevertheless, other ætiological factors are certainly of importance, and these will now be discussed.

Sedentary life.—Prosperity certainly leads to a reduction in the amount of manual work done by members of a community. As the wealth of a country increases, the ‘ pick and shovel ’ men decline and are replaced by those who flick switches and occupy office chairs. An increase in private cars and public transport reduces the number who rely on walking and the push bicycle to get them from place to place. There is some evidence that physical activity protects against ischæmic heart disease. There are occupations in which the risk of developing ischæmic heart disease is less than in others. Thus Morris and his colleagues (1953) showed that London bus conductors (on double-decker vehicles) have a lower incidence than bus drivers, and postmen who deliver letters have a lower incidence than telephonists and post-office clerks. Further, when atherosclerotic disease was present in conductors and postmen, it was less severe. Morris and Crawford (1958) in a national survey in Great Britain correlated the extent of the atherosclerosis found in the coronary arteries at post-mortem with previous occupation. They conclude that physical activity at work is a protection against ischæmic heart disease. ' Men in physically active jobs have less coronary heart disease during middle age, what disease they have is less severe, and they develop it later than men in physically inactive jobs.'

As described in Chapter 6, it is possible to eat large amounts of animal fats without a rise in plasma cholesterol, provided sufficient physical exercise is taken. There is no doubt that physical activity in general lowers plasma cholesterol levels and so may protect against atherosclerosis.

Stress and strain.—It is often suggested that the stress and strain of modern life predispose to atherosclerosis. The stress and strain to which the prosperous business executive or professional man is exposed are well known. A cartoon in the *New Yorker* showed two middle-aged men in shorts on the verandah of a luxurious holiday hotel. One says to the other " If I were the type to relax could I afford to be here ? " The stress and strain of poverty receive much less publicity, but perhaps only a minor proportion of the poor rest contented with their lot. It is difficult to be certain that the modern prosperous communities suffer from more stress and strain than their less wealthy predecessors. We know of no satisfactory evidence that any particular psychological type of individual is especially prone to atherosclerosis.

However, there is no doubt that once atherosclerosis is established, emotion, especially anger, can be the immediate cause of clinical symptoms. Long ago the great anatomist, John Hunter, who suffered from angina pectoris, said that he was at the mercy of any knave who chose to enrage him. More recently Eisenhower has related how his symptoms of coronary thrombosis developed on the golf course when for the third time in one morning he was recalled to the clubhouse to answer an unnecessary telephone call from the State Department.

Smoking.—There is evidence that heavy cigarette smokers are more prone to ischæmic heart disease than others (Hammond & Horn, 1954 ; Doll & Hill, 1954 ; Dawber *et al.*, 1957). Cigarette smokers in Finland have a higher plasma cholesterol level than non-smokers (Karvonen *et al.*, 1959), but the evidence available does not justify the claim that smoking causes the difference. Smoking would appear to be a doubtful contributory cause of atherosclerosis, but may well be of considerable importance in the production of its clinical complications.

Heredity.—That those who wish to enjoy a calm old age should choose their parents carefully is sound advice which has been given for generations. Families in which several male members have died from arterial disease in early middle age or before are known to most physicians.

The uncommon skin disease, xanthomatosis, in which nodules containing cholesterol appear in large numbers in the skin, has been known for a long time to be a familial disorder. Only comparatively recently has it been shown that this skin manifestation is part of a generalised disturbance of cholesterol metabolism in which the plasma level is raised markedly. The disease is now known as familial hypercholesteræmia. There is a very high incidence of deaths from heart disease in early life in men from such families. The disease is probably due to the presence of a gene which is incompletely dominant (Adlersberg & Schæfer, 1959). Perhaps hypercholesteræmia with or without atherosclerosis (but without xanthomatosis) represents the heterozygous state of the gene. The gene may be much more common than was previously considered likely, but ' penetration ' or the expression of its activity may be masked. Penetration might increase with age or under various environmental conditions. Schæfer *et al.* (1958) showed that there is a significant correlation between the plasma cholesterol levels of children and their parents (due allowance was made for age) in a series of New York families.

It is probable that the recent interest in diet as an ætiological factor has led to underemphasis of the importance of heredity in determining the incidence of atherosclerosis.

Associated diseases.—*Hypertension and obesity.*—Clinicians have for a long time held the view that ischæmic heart disease and other clinical evidence of atherosclerosis arises more commonly in patients who have high blood pressure or who are obese. This view has been supported by the results of the Framingham study. Framingham is a small town in New England where a continuous study of the incidence of heart disease has been in progress since 1948 (Dawber *et al.*, 1957 ; Kannel *et al.*, 1961). Out of 1333 men aged 40 to 59, 96 developed atherosclerotic heart disease during a 6-year period and the overall incidence rate was 72 per 1000. In those who had a normal blood pressure, a low plasma cholesterol and a normal electrocardiogram, the incidence rate was only 36 per 1000. If blood pressure was raised it rose to 91 and if the plasma cholesterol was raised, to 121 ; if both these factors were adverse it was as high as 154. These figures show in a striking manner how a high blood pressure and a raised plasma cholesterol predispose to ischæmic heart disease. Other figures show the importance of obesity in predisposing to the disease. At present it is not possible to state whether this is due to an accelerating action on the development of the atherosclerotic lesions or to an increasing liability to thrombosis and other complications.

Endocrine factors.—Ischæmic heart disease is about ten times as common in men than in women up to the age of 45. After the menopause there is a greatly increased incidence in women, and by the age of 70 there is no difference between the sexes. The relative immunity of women during their reproductive life is almost certainly due to the secretion of the ovarian hormones. As already described in Chapter 6, the level of plasma cholesterol is much lower in women aged 20 to 45 years than in men of the same age group. If both ovaries are removed before the age or 35, this is often followed by a rise in plasma cholesterol and the incidence of ischæmic heart disease is greatly increased.

Diabetics, especially if their disease is inadequately controlled by insulin, and patients with thyroid deficiency (myxœdema) have a greatly increased liability to atherosclerotic disease. This again is associated with changes in plasma lipids and a high cholesterol level.

The importance of the normal secretion of the thyroid gland in preventing ischæmic heart disease is suggested by the observations of Uotila, Rækallio and Ehrnrooth (1958). They compared the weights of the thyroid gland obtained at post-mortem in 250 subjects with ischæmic heart disease and in 250 controls. Table 40, 2 gives the results. The larger mean weight of the glands in ischæmic heart group may indicate a relative failure of secretion associated with incipient or actual simple goitre. In detailed epidemiological studies in Finland it has been shown that in those districts where colloid goitre is high, there is also a high incidence of ischæmic heart disease. These results may explain the position of Finland at the top of the list for European countries (Table 40, 1).

TABLE 40, 2. *The mean weights of the thyroid gland obtained at post-mortem from* 250 *patients with ischæmic heart disease and in* 250 *controls*

	Weight of thyroid gland (g.)	
	Ischæmic heart disease group	Control group
Males	50·3	37·8
Females	46·6	35·0

(These differences are significant, P = 0·001 for males and 0·01 for females.)

Thus there is no doubt that endocrine imbalances affect both the fat transport system and the incidence of atherosclerotic disease. Oliver and Boyd (1958) give a full review of the subject.

Unfortunately hormone preparations are as yet of no value in treatment (p. 559).

Summary.—The way social and economic factors present in a prosperous community may lead to atherosclerotic disease is illustrated in Fig. 40, 1. This scheme was drawn up by Oliver and Boyd in 1956. Six years later it remains a valuable summary, but the canny label is still necessary. Many of the stages are still speculative. The enthusiast is still, as always, apt to mistake ‘ associations ’ for causes.

The hypothesis that dietary fat is a primary factor in the ætiology of atherosclerotic disease and the consequent implications have been well summed up by Bronte-Stewart (1961) as follows :

> Trends in modern diets of the western industrialised nations over the past few decades have allowed an increase in the consumption of saturated fatty acids at the expense of or without a sufficiently concomitant increase of the polyunsaturated fatty acids. The dietary fat hypothesis implies that this leads to a disordered lipid metabolism which over the years leads to atherosclerosis and possibly is one of the major contributing factors to the final picture, ischæmic heart disease. These implications are wide, affecting developments in animal husbandry, food processing and the health education of our youth. For these reasons it is perhaps desirable to demand a great deal more factual information before widespread application is practised. Nevertheless, if one accepts that an environmental factor is at the background of the alarming increase in mortality from ischæmic heart disease, of all those that constitute our present-day mode of life no other at present known can be so closely related to pathological, metabolic and epidemiological features of the disease as the nature of the dietary fat intake.

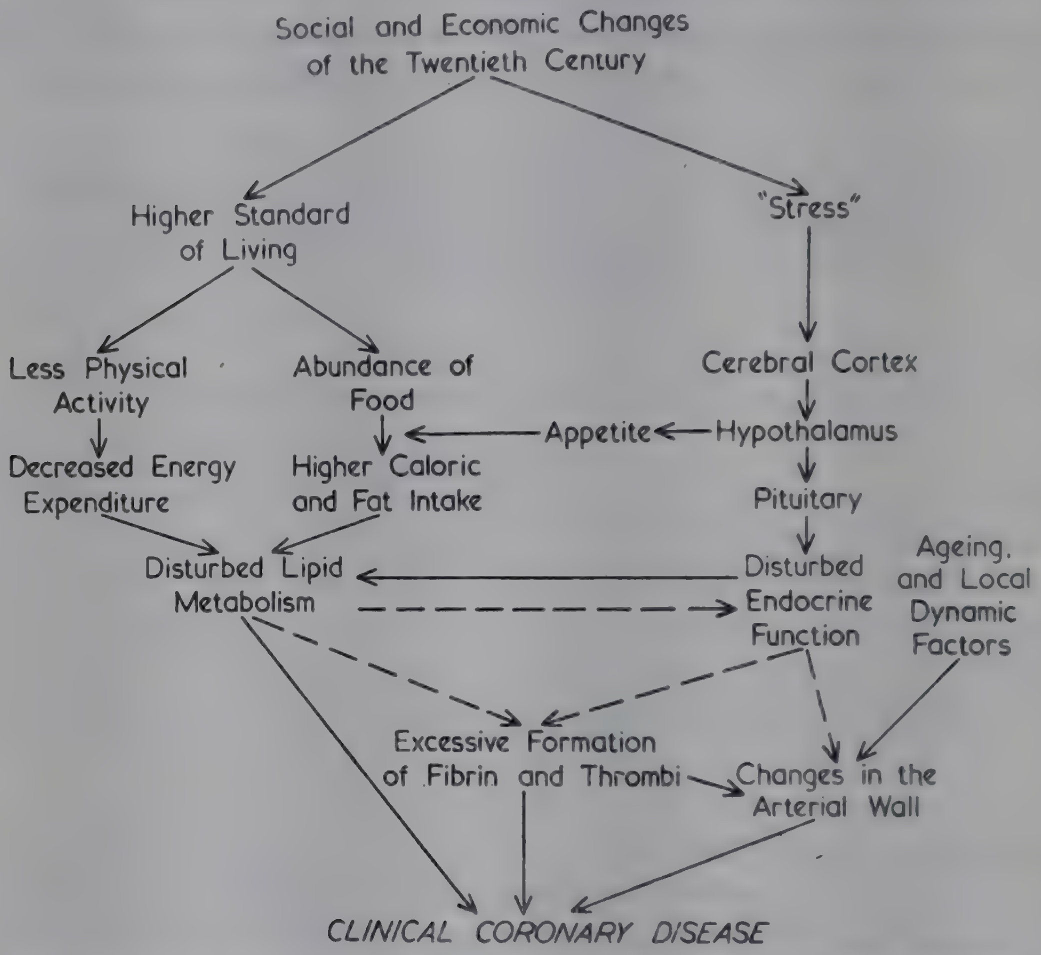
Social and Economic Changes of the Twentieth Century
Higher Standard of Living
"Stress"
Less Physical Activity
Abundance of Food
Cerebral Cortex
Appetite
Hypothalamus
Decreased Energy Expenditure
Higher Caloric and Fat Intake
Pituitary
Disturbed Lipid Metabolism
Disturbed Endocrine Function
Ageing. and Local Dynamic Factors
Excessive Formation of Fibrin and Thrombi
Changes in the Arterial Wall
CLINICAL CORONARY DISEASE

FIG. 40, 1. A speculative scheme showing possible associations between the twentieth century environment and clinical coronary artery disease. (Oliver and Boyd, 1956)

We would not dissent from anything in this clear statement. However, we believe that a sedentary life and reduced physical activity may be just as important as changes in the intake of dietary fats. Proof that the association is one of cause and effect is equally lacking for both.

PREVENTION AND TREATMENT

As already pointed out, it is impossible to assess accurately the progress of atherosclerosis in the arteries of an individual or a group of individuals. Only the incidence of the clinical complications can be determined and recorded. However, two questions must be asked (Oliver, 1962). (1) Is reduction of elevated plasma lipids in otherwise healthy individuals likely to postpone or prevent the development of ischæmic heart disease in them ? (2) Is reduction of elevated plasma lipids to levels present in apparently healthy individuals likely to benefit patients who already have established ischæmic heart disease ? Oliver attempts an answer to these questions and concludes that at the moment it is quite impossible to answer ' Yes ' to either of them. In regard to question 1 it should be noted that any trial designed with the object of testing the prophylactic value of any therapeutic measure would necessitate the follow-up of many hundreds of apparently healthy individuals for a period of 5 years or longer, if results of any value were to be obtained. This presents great practical and ethical difficulties as is clearly indicated by Oliver. These difficulties explain why such evidence is not available at the time of writing. With regard to question 2 in two studies, one in Edinburgh (Oliver & Boyd, 1961) and one in Chicago (Stamler *et al.*, 1960), a substantial lowering of the plasma lipids, lasting for several years, was effected by means of œstrogen therapy in groups of men who had survived a myocardial infarction. Both in Edinburgh and in Chicago the incidence of further myocardial infarction was the same in the treated group as in an untreated control group. A lowering of the plasma lipids, at least by this method, appeared to confer no benefit on these patients.

Diet.—Is it possible by dietary measures to prevent or slow down the development of atherosclerosis in man ? To this question there is only one answer. We don't know. Is the evidence implicating the dietary fats in the causation of atherosclerosis sufficient to justify physicians recommending dietary restrictions of any sort ? Different answers to this question will be given by different physicians according to their interpretation of the circumstantial evidence, which has already been reviewed.

Those physicians who do not accept the evidence indicating that dietary fats are important in the pathogenesis of atherosclerosis will obviously refuse to inconvenience their patients by any dietary restriction of animal fats.

On the other hand physicians who are impressed with the evidence will insist that the intake of animal fats be restricted in certain groups of people.

GROUP 1.—Individuals leading sedentary lives who have reached middle age would be instructed to limit their fat intake to 25 to 30 per cent. of their total calories instead of the 40 per cent. or more which is not unusual in a prosperous community. This advice does not involve material changes in traditional food habits or ‘ crackpot ’ diets. In simple language such persons should be advised to limit their intake of butter, cream and pastries. Fried foods should be a luxury rather than a regular feature of their diets. Bacon and eggs for breakfast should be taken exceptionally and not regularly. They should choose lean portions of bacon, ham, beef or mutton and remove all excess fat. Vegetable oils, such as corn oil, sunflower seed oil, but not olive oil or coconut fat, rather than animal fats should be used for cooking where possible.

This regime would be recommended in the hope that it may do good and in the knowledge that it can do no harm and can be carried out without difficulty and without causing any real hardship. In addition these measures will help to prevent the development of obesity, the harmful effects of which have been described in Chapter 27.

GROUP 2 includes all patients with the clinical sequelæ of atherosclerosis except those who are at special risk as indicated in Group 3. Patients in Group 2 would be given the same dietetic instructions as those in Group 1.

GROUP 3 includes patients who are known to be at considerable risk of dying from the myocardial infarction ; these are men under 50 with a high plasma cholesterol and a strong family history of degenerative vascular disease, and especially if obesity or hypertension is also present. For such persons there is a strong case for reducing drastically the level of the plasma cholesterol, and for this purpose much greater restriction of animal fats and their replacement as far as possible by vegetable and marine oils must be enforced. Diets No. 12A and No. 12B and the accompanying instructions will show how this can be achieved.

These dietary restrictions will have to be continued for years and possibly for life. Because of the psychological and domestic difficulties which may arise, the decision to prescribe such a diet should only be taken by a physician experienced in this particular problem and one who can obtain the help of a dietitian for instructing the patient in the selection of foods for the low fat diet and in the appropriate methods of cooking with vegetable oils.

Physical exercise.—There is no doubt that the development of atherosclerosis is associated with sedentary life as is obesity (p. 382) ; also in some circumstances physical exercise lowers the level of plasma lipids. Hence all persons liable to develop the clinical sequels of atherosclerosis as well as those who already have established disease should be advised to take regular physical exercise. Obviously activities which cause undue fatigue, breathlessness or palpitations must be avoided. Walking is specially to be recommended, as are recreations such as golf, gardening and swimming, provided they are carried out sensibly and in moderation.

Hormonal therapy.—Many œstrogen preparations and thyroxine and its analogues will lower the plasma lipid levels. There is, as already stated, no evidence that this lowering produces any clinical benefit.

There is at the time of writing no preparation of either hormone that will lower the plasma lipids with a dosage that will not also cause undesirable side-effects. In the case of thyroid hormones, the stimulating effect on the heart is particularly dangerous. For these reasons hormonal therapy for atherosclerosis is contraindicated, unless there is evidence of a hormonal deficiency.

Œstrogens should be given to women who have had their ovaries removed in early life and this should reduce their liability to atherosclerotic disease. The sooner patients with thyroid deficiency are diagnosed and receive hormonal therapy, the less likely they are to develop atherosclerosis. Diabetics will benefit similarly if their disease is carefully controlled by diet, and, if necessary, insulin.

Treatment of associated diseases.—A most important role of the physician both in the prevention and treatment of atherosclerosis is to see that the associated diseases are energetically treated. Obesity, hypertension, diabetes and thyroid deficiency all lead to atherosclerosis. These are diseases that can, at least, be controlled. Their importance as atherosclerotic agents has been too often overlooked.

ARTERIOSCLEROSIS

Arteriosclerosis is a term which in the past has been applied rather indiscriminately to various forms of degenerative arterial disease. As age advances, the arteries gradually lose their elasticity and are said to harden. Degenerative changes take place in the medial wall with disruption of the muscle fibres and overgrowth of connective tissue. Later the intima is also involved, the lumen becoming narrowed to a degree which varies with the size of the affected vessels and the degree of hypertension present. Medium and small vessels are especially involved.

Atheromatous degeneration in the intima is frequently found in vessels which are the seat of arteriosclerosis, but the two conditions can arise independently of each other and they appear to be distinct pathological processes.

Arteriosclerosis is a degenerative condition which develops perhaps as a compensatory mechanism to the gradual increase in intra-arterial pressure which occurs with advancing years, and hence may be considered as a natural ageing process.

Arteriosclerotic changes are greatly accelerated by hypertension which may be said to cause the disorder to progress from a physiological to a pathological state. The ætiology of arteriosclerosis is not fully understood, but there is no satisfactory evidence that diet plays any significant part in its development. Genetic factors are certainly important. Members of some families are notoriously long-lived, while in other families the expectation of life is relatively short. These variations can be attributed largely to the rate at which degenerative changes develop in the arterial walls—the quality of the ' vital rubber.'

Treatment.—If arteriosclerosis is associated with hypertension or congestive heart failure, treatment must be initiated along the lines described on pages 564 and 566. Otherwise there is no specific treatment, but the general dietary advice for people of middle age (p. 559) is applicable.

MEDIAL SCLEROSIS (MÖNCKEBERG'S SCLEROSIS)

This affects the muscular coats of medium-sized peripheral and superficial arteries and is responsible for the ' pipe stem ' arteries commonly found in old age. Calcification of the media is the characteristic change. There is no evidence that dietary factors play any part in its ætiology. Although the arteries are rigid, their lumina are not significantly narrowed. No treatment is available or necessary.

PERIPHERAL VASCULAR DISEASE

The term ' peripheral vascular disease ' is used to describe the characteristic clinical picture which develops when the blood supply to the limbs is impaired.

Peripheral vascular disease may be suggested by pain and swelling or by changes in colour, temperature or arterial pulsation in the extremities. These disturbances may result from organic obstruction of the vessels secondary to obliterative disease or from changes in vasomotor tone leading to vasoconstriction or vasodilatation. Obliterative disease and vasoconstriction are often associated.

The principal cause of obliterative disease is atherosclerosis, the pathogenesis, prevention and treatment of which have already been discussed. Symptomatic treatment consists of protection of the affected parts from cold and trauma. Vasodilator drugs are of little value. Surgical sympathectomy is indicated in selected cases.

The two most common peripheral vascular diseases due to vasoconstriction are Raynaud's disease and chilblains. The vasospasm is precipitated by cold and sometimes by emotion. It may also result from high-frequency vibrations set up by pneumatic drills. Chilblains are due to local areas of vasospasm and vasodilation. Treatment of the above disorders consists primarily in protecting the affected parts from cold. Vasodilator drugs are disappointing. Nutritional deficiency plays no significant part in their development, so it is not surprising that dietetic treatment, including calcium, vitamin D and nicotinic acid, which are widely used in these disorders, is of doubtful value.

ESSENTIAL (IDIOPATHIC) HYPERTENSION

In the majority of cases of hypertension the cause is obscure, and for these the term ' essential,' ' primary ' or ' idiopathic ' hypertension is used. In a minority of cases the hypertension is secondary to various renal and endocrine disorders. Management of secondary hypertension includes the treatment of the underlying disease and measures for lowering the blood pressure as discussed for the treatment of essential hypertension.

In healthy young adults the systolic blood pressure is about 120 mm. Hg and the diastolic pressure about 80. There is usually a gradual rise of blood pressure as age advances and at 65 years the mean figure is about 160/90. The rise with age is very variable. In some people it is more rapid and reaches a higher level than the above figure. It is difficult to state at what point the level ceases to be normal and hypertension begins. The diastolic pressure is a more reliable guide to the presence or absence of hypertension than the systolic pressure. Mild hypertension may be said to be present when the diastolic pressure is 90 to 110, moderate hypertension when the diastolic pressure is 110 to 130 and severe hypertension when the diastolic pressure exceeds 130. When severe hypertension is associated with renal failure or papillœdema, the condition is sometimes called ' malignant hypertension.'

In some individuals there is no rise of blood pressure as age advances. This is indeed the case amongst people who lead primitive lives. Low blood pressures in middle age are the rule in many parts of Africa.

In New Guinea (White, 1958) and in two Pacific Islands (Maddocks, 1961), there is little or no change in the blood pressure of the natives with advancing age. They do not suffer from hypertension, which is a disease of civilisation.

The causes of the gradual rise in blood pressure which usually occurs with advancing age and the excessive rise which develops in some patients are not fully known. Of various possibilities, genetic factors are certainly important. The blood pressure appears to be inherited in much the same way as height (Pickering, 1961). However, genetic factors cannot account for all the variations.

Environmental factors are also responsible. Two which may operate in some patients are dietary in origin. An excessive caloric intake leading to obesity is often associated with hypertension. However, Bøe *et al.* (1957) in Norway found that the relation between body weight and blood pressure was very slight, when the effect of age was allowed for. Certainly thin people may also develop hypertension.

It is well known (see below) that a low salt diet causes a marked reduction of blood pressure in patients with hypertension. In those parts of Africa and Asia, where the blood pressure usually remains low in middle age, the supply of salt is often limited and individual daily intakes are much lower than is the custom in Europe and America. These facts have led some to postulate that a high intake of salt leads to hypertension ; yet it is difficult to measure the salt intake either of individuals or nations, and epidemiological studies which attempt to relate high blood pressure with a high salt intake have not been convincing.

Psychological factors often cause an immediate and temporary rise in blood pressure, but whether the stress and strain of life can be held responsible for permanent rises is uncertain. Many patients with anxiety states have normal or even low blood pressures and many well-balanced individuals become hypertensive.

Certainly hereditary, dietary or psychological factors cannot explain satisfactorily the incidence or causation of hypertension. Other factors—renal, vasomotor and hormonal—are probably important. These are fully discussed in Sir George Pickering's monograph.

Treatment.—This is unsatisfactory because there is no specific remedy, and hence, at present, no possibility of cure.

MILD HYPERTENSION (DIASTOLIC PRESSURE 90 TO 110).—The condition may be found accidentally in the course of a life insurance or routine medical examination and the patient may complain of no symptoms, in which case no mention of the finding should be made to the patient and no treatment given.

MODERATE HYPERTENSION (DIASTOLIC PRESSURE 110 TO 130).—The common symptoms are headache, cardiac discomfort and breathlessness. These are often improved by simple dietary treatment and advice. If the patient is overweight, treatment of the obesity so as to bring about a loss of 2 to 3 lb. (1 to 1·5 kg.) a week often relieves the symptoms and brings about a significant fall in blood pressure. There is nothing to be gained by severely restricting the intake of protein, or the prohibition of red meat, and alcohol in moderation should be allowed. The treatment of obesity is very important since the chance of developing ischæmic heart disease is greatly increased if hypertension and obesity coexist. Many patients need to be told how to organise their lives so as to avoid emotional stress and excessive physical activity. They should be advised to take proper holidays, enjoy suitable recreations, take regular meals and find time to eat them leisurely. Sedatives and tranquillising agents are often useful. Moderation in all things is the guiding principle to be adopted.

If these simple measures are not sufficient, hypotensive drugs should be given. Rauwolfia and its derivatives (*e.g.* reserpine) alone or in combination with chlorothiazide, are useful and are the first drugs to be tried in the treatment of moderate hypertension.

SEVERE HYPERTENSION (DIASTOLIC PRESSURE OVER 130) AND MALIGNANT HYPERTENSION.—For patients with moderate hypertension who have failed to respond to the measures discussed above, and for patients with objective evidence of severe hypertension, namely disease of the heart, retina, kidneys or peripheral arteries, three additional lines of treatment are available :—

1. *Ganglion blocking drugs* can effectively lower the blood pressure by paralysing the autonomic nervous control of the blood vessels. Mecamylamine and pempidine, which block the transmission of both sympathetic and parasympathetic impulses, and drugs such as methyldopa and guanethidine, which block selectively the peripheral sympathetic nervous system, have been widely used. There is no hypotensive drug that is entirely satisfactory, as all have unpleasant or serious side-effects. Nevertheless, at the time of writing such drugs offer the best hope of controlling severe

hypertension. Until it has been shown that in a particular case they have failed, surgical operations should not be considered.

The hypotensive effects of ganglion blocking drugs and of rauwolfia derivatives may be enhanced by the use of one of the thiazidine diuretics, of which chlorothiazide was the first to be synthesised. This drug, which is given by mouth, increases the excretion of sodium and chloride in about equimolar amounts.

2. *Decreased intake and increased excretion of sodium.*—If the sodium content of the body is significantly reduced there is usually a fall in blood pressure and relief of the symptoms. This can often be achieved by the use of the restricted salt regimen (p. 571) provided it is combined with the administration of chlorothiazide which greatly increases sodium excretion. Only if these measures fail should the minimum sodium (rice-fruit) diet (No. 15) be tried. This will usually bring about a marked fall of blood pressure. This diet contains less than 0·2 g. (9 mEq.) of sodium. As this diet is extremely unappetising and cannot be tolerated by most patients for long, it should not be recommended for general use. However, in an emergency, as when sight is threatened by advancing papillœdema or there is grave cardiac failure, and when hypotensive drugs have failed, 3 to 6 weeks on the diet will usually substantially reduce the blood pressure and may cause marked relief of symptoms and signs.

It should be remembered that sodium restriction depresses renal function and there is a danger that it may precipitate uræmia in patients whose kidneys are already damaged.

3. *A variety of surgical operations* on the sympathetic nervous supply of the blood vessels have been devised. Bilateral adrenalectomy is also sometimes performed. These operations will bring about an immediate fall in blood pressure and generally some clinical improvement. Unfortunately this is often transitory. As the surgical procedures are major operations, they should be reserved for patients with severe hypertension who have failed to benefit from the measures discussed above.

CARDIAC DISEASE

The approximate incidence of the various forms of cardiac disease in Great Britain is as follows :—

	Per cent.
Ischæmic heart disease (coronary atheroma) Hypertensive heart disease	55
Rheumatic heart disease	25
Pulmonary heart disease	10
Congenital heart disease	3
Thyrotoxic heart disease	1
Syphilitic heart disease	1
Other forms of heart disease	5

Ischæmic heart disease and hypertensive heart disease are of particular importance in middle and old age and are becoming increasingly frequent, while rheumatic fever is by far the most common cause of cardiac disease in childhood, adolescence and early adult life, and its incidence and severity are steadily falling.

ISCHÆMIC HEART DISEASE

The two most important factors leading to ischæmic heart disease are damage to the walls of the coronary arteries by atherosclerosis and increased liability of the blood to form a thrombus. The pathology, epidemiology, prevention and treatment of these factors have been discussed in detail on pages 548 to 561, to which the reader is referred for information on low fat diets, physical exercise, endocrine and other factors, relevant to the prevention and treatment of ischæmic heart disease.

There remains to be described the treatment of patients immediately after myocardial infarction has occurred. This must be directed to the relief of pain, shock and cardiac failure. Thereafter rest in bed is necessary whilst a firm fibrous scar forms in the damaged area of the heart muscle. This should be for a minimum period of 3 weeks, but 6 weeks or more may be necessary after a large infarction or if cardiac failure has developed.

In order to reduce the likelihood of a recurrence or an extension of the thrombosis, anticoagulant drugs have been widely recommended.

Heparin, a natural anticoagulant (p. 52), is used to reduce the clotting time of the blood. Its action is rapid but transitory and it has to be given parenterally. Hence treatment is continued with the coumarin group of drugs which can be given orally and which have a more prolonged action. Drugs of this group, such as phenindione, are antagonists of vitamin K (p. 209). By preventing the normal action of this vitamin, the prothrombin time, as estimated by Quick's method, is prolonged and the blood clots less readily.

If immediately after infarction has taken place the clinical features of congestive heart failure are present, treatment must be started on the appropriate lines as described on page 568.

DIETARY MEASURES.—Sometimes the infarction is of such limited extent that the patient develops neither shock nor cardiac failure. For such patients, and also for those who have recovered from cardiac failure, an ordinary light diet can be given until the question as to whether an attempt should be made to lower the plasma cholesterol level by dietary means, in the hope of preventing a recurrence, has been decided. This problem has been discussed in detail on page 559 in the section on Atherosclerosis.

As long as complete bed rest is enforced, energy expenditure will be little above basal levels and probably below 2000 Cal./day. Hence the caloric value of an ordinary hospital diet should be reduced by giving small helpings. It is important that obesity should not be allowed to develop.

VALVULAR DISEASE OF THE HEART

The most important cause of valvular disease of the heart is rheumatic fever. The valve most commonly affected is the mitral valve and much less frequently the aortic or tricuspid valves.

Syphilis affects the first part of the aorta (syphilitic aortitis) and may involve the openings of the coronary arteries causing ischæmic heart disease, and also the aortic valves, leading to aortic incompetence and cardiac failure. Syphilitic heart disease is now rare because of the measures which have been taken to educate the public on the need for early diagnosis and efficient treatment. Penicillin can be guaranteed to cure syphilis completely if treatment is adequate.

Subacute bacterial endocarditis and ulcerative endocarditis were diseases which were almost invariably fatal prior to the discovery of penicillin and other antibiotics. Early and adequate treatment leads to a high incidence of cure.

Congenital lesions are an important cause of disease of the pulmonary valves and of septal defects. Surgical techniques have improved the prognosis of congenital heart disease and some valvular lesions.

PULMONARY AND THYROTOXIC HEART DISEASE

In industrial regions where the pollution of the air is marked, chronic bronchitis and emphysema are common diseases. In such areas the incidence of pulmonary heart disease (cor pulmonale) is greater than that given on page 565. Smoking in excess is another important factor in the causation of chronic bronchitis and emphysema. Prophylactic measures by local authorities to reduce the pollution of the air and to disseminate information about the dangers of smoking, and the intelligent use of antibiotics in both acute and chronic pulmonary infections are of great importance. Eventually many of these patients develop congestive cardiac failure.

Thyrotoxicosis in middle-aged and elderly persons, if unrecognised and so not treated, ends not infrequently in congestive cardiac failure often associated with atrial fibrillation. This sequel should rarely occur at the present time since the underlying cause can be brought under control by medical measures (antithyroid drugs), surgical measures (partial thyroidectomy) or by irradiation (radioactive iodine). If congestive cardiac failure develops, treatment as outlined overleaf should be instituted.

Comment.—With the possible exception of rheumatic fever, which affects the poor far more frequently than the well-to-do, there is no satisfactory evidence that nutritional deficiency plays any part in the ætiology of the forms of heart disease discussed above or that any special diets are required for their treatment other than those used for the correction of obesity if present or the treatment of congestive cardiac failure which usually develops in time.

CONGESTIVE HEART FAILURE

In severe congestive heart failure the patient is completely incapacitated. The slightest exertion causes extreme breathlessness and generalised œdema is present owing to increased venous pressure and retention of sodium, secondary to reduced renal blood flow.

In mild to moderate congestive failure the condition has not progressed so far, or partial recovery may have taken place. Breathlessness is present on effort and œdema of the ankles is noticeable in the evening.

Treatment.—As has already been indicated congestive heart failure may be the terminal event in hypertensive, ischæmic, valvular, pulmonary or thyrotoxic cardiac disease. Irrespective of the cause, the aim of treatment is to secure the maximum of rest for the heart and to remove the œdema. The basis of treatment is (1) complete rest, (2) the administration of diuretics (mersalyl, chlorothiazide) and cardiac stimulants (digitalis), and (3) a diet low in sodium and in calories.

The diet in congestive heart failure should be constructed on the following principles :—

1. As the œdema fluid has the same sodium concentration as plasma, œdema is always associated with retention of sodium. In severe œdema the excess fluid retained may amount to 10 *l.* or more, containing 1400 mEq. of sodium, equivalent to over 80 g. of sodium chloride. The removal of this is greatly facilitated if the sodium intake is reduced. Practical details of how to reduce the sodium intake are given on pages 570 to 572.
2. Rigid restriction of the fluid intake, as was formerly recommended, is not necessary if the intake of sodium is adequately reduced and its excretion increased. Sufficient fluid to quench thirst and make the patient comfortable, *i.e.* up to 2 *l.* daily, may be allowed.
3. The caloric intake must be low, since any food intake will stimulate metabolism and increase the work of the heart.
4. Owing to the congestion of the digestive organs, each feed must be small in quantity and easily digestible. In the initial treatment, fluid or semi-fluid food is advisable for patients who are seriously ill.

Dietary Management of Cardiac Failure

For most patients with mild or moderate degrees of cardiac failure the restricted salt regime described on page 571 will be suitable.

For the severe grades of failure, the Karell fluid diet has been recommended. This is simple and effective. It consists of 800 ml. of milk, given in four feeds, each of 200 ml. (one small glass). No other food or fluid is given. It provides about 550 Cal., 28 g. protein and about 0·45 g. (20 mEq.) of sodium. This diet should only be employed for 2 or 3 days as the patient will complain of monotony and thirst.

Alternatively the patient can start with the light diet (Diet No. 13) which provides about 900 Cal., 20 g. protein and 1 g. (45 mEq.) of sodium. No table salt should be added.

Diet No. 15, the minimal sodium (rice-fruit) diet, is seldom required for the treatment of congestive cardiac failure.

Occasionally patients with severe congestive failure are encountered whose response to digitalis, diuretics and a diet low in sodium is negligible. Such resistance to treatment is sometimes due to excessive production of aldosterone which has a marked effect in increasing the absorption of sodium from the renal tubules. The administration of the aldosterone antagonist, spironolactone, may produce a dramatic sodium diuresis, especially when given concurrently with chlorothiazide.

With improvement in the clinical condition a light ward diet can be given, but the salt intake must still be restricted. The restricted salt regime will keep the sodium intake to about one-third of normal.

Compensated Heart Disease

When recovery has taken place or in less severe cases, the patient may be up and about and able to continue his normal occupation. Heart disease, however, always involves some curtailment of physical activities, and the more arduous recreations must be given up. This reduction in energy expenditure must always be balanced by a corresponding reduction in food intake. If the diet is not reduced appropriately, obesity will inevitably follow. Obesity is common in patients with heart disease. It is, in fact, a serious complication for it interferes with cardiac efficiency in three ways :—

1. The increased body weight due to the deposition of fat leads to a lack of balance between the body mass and the heart's action, and therefore adds to the work of the heart.
2. Fatty changes may occur in the heart, which impair its efficiency. The epicardial fat becomes excessive, and fat may be deposited between the muscle bundles.
3. The accumulation of fat within the abdomen interferes with the movements of the diaphragm and thus impairs the action of the heart.

The increased body weight and the cardiac embarrassment limit the patient's activities, and as this is usually not accompanied by a lessened food intake, further accumulation of fat completes a vicious circle.

The treatment of obesity, if present, is most important ; it follows the lines already set out in Chapter 27. In the absence of obesity, dietary restrictions are unnecessary and indeed contraindicated because of the harmful psychological effects induced. The following guiding principles may be helpful as part of the general reorganisation of the patient's method of living. Meals should be regular, well spaced and light. Bulky foods containing large amounts of cellulose should be reduced to a minimum. Indigestible foods such as pastries, rich cakes or puddings, pickles, preserved or salted meats, or fried foods should be avoided, or taken only in small amounts. The evening meal should always be light and should be taken early. The patient should be instructed to eat his food slowly and masticate thoroughly. Every meal should be preceded and followed by a rest. Digestive upsets must be guarded against, especially if any degree of chronic venous congestion is present, since the digestion and utilisation of the food is impaired by congestion of the gastric mucosa and the liver. Cardiac failure or angina pectoris may be precipitated by over-eating or flatulence. The rules laid down above will help to prevent digestive upsets. If flatulence is present, the starchy foods of the diet should be reduced.

When there is no œdema, restriction of salt and fluid is unnecessary. Tea and coffee may be taken in moderate amounts.

DIETS LOW IN SALT

The terms *restricted salt regime*, *low sodium diet* and *minimal sodium* (*rice-fruit*) *diet* are clearly defined in this section in order to avoid repetition and duplication; they are used with the same exact meaning in other chapters of this book.

Table 40, 3 gives the sodium content of the regimes expressed in three different ways. Unfortunately each is often used indiscriminately by writers of textbooks, physicians, dietitians and laboratory workers. It is therefore very important to make certain that in any discussion of the sodium content of a diet or article of food the unit is clearly stated.

TABLE 40, 3. *Approximate daily intake of sodium on different regimes*

	Sodium expressed as		
	mEq.	g. Na	g. NaCl
A normal diet	100–300	2·3–7·0	6–18
Restricted salt regime . . .	40–80	1·0–2·0	2·5–4·0
Low sodium diet No. 14 . .	11–22	0·25–0·5	0·75–1·25
Minimal sodium (rice-fruit) diet No. 15	Below 9	Below 0·2	Below 0·5

Table 10, 3 (p. 144) gives a short list of the sodium content of foodstuffs divided into rich, moderate and poor sources. It is important to remember that almost all processed and manufactured foods have salt added. This is one of the oldest methods of preserving foods and is still much used. Such preserved foods, which include everything bought in a tin or bottle, should be presumed to be rich in sodium chloride unless specifically known to be otherwise. Cereal products, *e.g.* bread, breakfast cereals, biscuits and cakes, are almost always rich in sodium ; but most fresh unprocessed foods, *e.g.* meat, fish, eggs, milk and vegetables, are moderate sources ; fruits and natural unprocessed cereals are poor sources.

The sodium content of all foods is subject to wide variations, and calculations of the salt content of diets based on tables are liable to an error of up to ±50 per cent. Uræmia may develop in a patient with cardiac or renal disease who is on a low salt diet. The doctor must constantly keep this danger in mind.

A restricted salt regime

It is possible to reduce the dietary sodium intake to about a third of normal by eliminating the use of all table salt, reducing cooking salt to a minimum and by suitable selection of foods. *A restricted salt regime* allows the diet to be chosen from normal foods, but the foods which are rich sources of sodium (p. 144) should be excluded as far as possible or reduced to a minimum.

For most patients *a restricted salt regime* is a hardship, but one which can be undertaken for weeks or months with self-discipline. For psychological reasons it may be wise to allow the patient an occasional indulgence in a food which is normally not permitted. The regime does not exclude the sharing of meals with one's family or friends, but it does involve the selection of suitable articles of food.

The following points must be firmly impressed on patients and may be given to them as a printed list :—

1. No table salt is permitted.
2. Salt used in cooking must be reduced to a minimum.
3. Salt-rich foods, such as ham and bacon, sausages, all tinned meats and fish, shell-fish, cheese, all sauces (except special home-made ones) and all biscuits and shop cakes must be avoided.
4. The maximum amount of ordinary bread allowed is five thin slices daily and the maximum amount of butter is 1 oz. daily.
5. Helpings of fresh meat, fish, potatoes and other root vegetables must be small.
6. One egg and 250 ml. (½ pint) of milk daily are allowed.
7. All fruits and nuts are permitted.
8. Sugar and jams, rice and sago are freely allowed.

A low sodium diet

With the use of special foods and dietary measures, the daily sodium intake can be reduced further to about one-tenth of normal (0·25 to 0·5 g. Na daily, Diet No. 14). Strict adherence to the diet is necessary if these low intakes are to be achieved ; the use of special salt-free bread and butter is essential. The provision of *a low sodium diet* is usually only possible for patients in hospital. If taken at home, expert dietary supervision and instruction are necessary. Salt-free bread and butter are not easy to obtain in many places. Salt-free bread may be made by following the instructions on page 841.

A limit must be put on the time during which a patient may be expected to remain on this *low sodium diet.* This is usually about 3 to 6 weeks. By this time if there is clinical improvement, he should be changed to the *restricted salt regime.* If there is no improvement, perseverance is useless and other therapeutic measures must be tried.

A minimal sodium (rice-fruit) diet

By restricting the diet to washed rice, fruit and fruit juices, as first advocated by Kempner (1945), it is possible to reduce the sodium intake to below 0·2 g. daily. Diet No. 15 is an example of such a diet. Most patients find this monotonous and unappetising diet an intolerable strain. Hence it is seldom recommended at the present time; however, such a diet has a limited role in therapeutics but should only be prescribed when other measures have failed, as already discussed in the treatment of hypertension.

CHAPTER 41

DISEASES OF THE KIDNEYS AND URINARY TRACT

ANATOMY AND PHYSIOLOGY

THE kidneys are each composed of approximately one million similar functional units called ‘ nephrons.’ Each nephron consists of a glomerulus which is a tuft of capillaries invaginated into an epithelial sac (Bowman’s capsule), from which arises a tubule. The blood flow through the kidneys is relatively large, amounting to about one-quarter of the cardiac output at rest, *i.e.* 1300 ml./min. Branches of the renal artery give rise to afferent arterioles which divide to form the glomerular capillaries. The capillaries then unite to form the efferent arterioles which in turn supply blood to the renal tubules.

The hydrostatic pressure within the glomerular capillaries results in the filtration of fluid into Bowman’s capsule. This fluid is identical in composition with plasma, except that it normally contains no fat and very little protein.

The filtrate, formed at the glomerulus, passes first into the proximal convoluted tubule and from there through the loop of Henle and distal convoluted tubule to the collecting ducts. It is modified according to the needs of the body by the selective reabsorption of its constituents and of water, and by tubular secretion. In health the volume and composition of the body fluids vary only within narrow limits ; such constancy is necessary for life and is maintained largely as a result of renal activity. The excretion of the waste products of metabolism represents merely one aspect of renal function which is also intimately concerned with the regulation of the water and electrolyte content of the body, the maintenance of the normal acid-base equilibrium of the blood, and the retention of substances vital to the economy of the body, *e.g.* amino acids, plasma proteins and glucose.

ASSESSMENT OF RENAL FUNCTION

Just as glycosuria does not necessarily indicate diabetes, so too protein in the urine does not invariably mean renal disease. Before proteinuria is accepted as being due to renal disease, other causes must be eliminated, especially the functional or orthostatic proteinuria of young people and the proteinuria of chronic venous congestion in elderly persons suffering from hypertensive heart disease.

Evidence of impaired renal function may be obtained by examining the urinary deposit for red blood cells and casts, or from the analysis of the blood for evidence of nitrogen retention. The simplest method of assessing the concentrating power of the kidney is by determining the specific gravity of the urine. If food and fluid are withheld for 12 hours, the specific gravity of the urine will be 1·028 or higher in young healthy persons and at least 1·022 in middle-aged or elderly persons. The ability to pass such a concentrated urine is evidence of healthy kidneys. Where very severe renal damage is present, the specific gravity of the urine becomes fixed at about 1·010. With lesser degrees of damage, the maximum specific gravity of the urine in this concentration test will lie somewhere between 1·022 and 1·010.

As failure of concentrating power is the earliest sign of renal damage, this test is suitable for the detection of the lesser degrees of impairment. It is only when the failure of concentrating power has progressed to a considerable extent that the concentration of nitrogenous substances in the blood begins to rise. The measurement of the specific gravity is only a rough test of renal function, and accordingly if there is any doubt about the condition of the kidneys, more precise methods must be used. These are beyond the scope of this book and are fully described in a monograph by Smith (1951).

Objects of dietetic treatment in nephritis

Once kidney disease has been established the next question is the aim of the dietetic measures that are to be employed. The diet should be so arranged as to—

1. *Spare the diseased kidneys* by minimising their work of excreting the end-products of metabolism.
2. *Prevent uræmia*, caused by the accumulation of waste products of metabolism : this tendency should be combated by reducing the amount of these waste products and by measures to promote their excretion by the damaged kidneys.
3. *Prevent œdema*, which is caused by retention of water and sodium.
4. *Maintain nutrition.* It is apt to be forgotten that chronic nephritis is essentially a wasting disease. Therefore the diet should have a caloric intake sufficient to maintain the patient's nutrition and should contain adequate quantities of protein, minerals and vitamins.

There is diversity of opinion about the value of diet in achieving these objects. There are some who believe that diet is the chief therapeutic weapon for all forms of nephritis ; others hold not only that there is little evidence that diet alters appreciably the course of progressive renal disease, but that rigid dietary restriction, especially of protein, does harm by lowering the patient's general condition and powers of resistance to infection. These conflicting views are at least partly due to a misconception of the metabolic changes caused by renal disease and partly to a failure to define clearly the aims of dietetic treatment in the different types or stages of nephritis. In the writers' opinion, apart from rest in bed and protection from cold, dietetic measures constitute the most important part of treatment in acute nephritis. In subacute and chronic nephritis with œdema, massive proteinuria and hypoproteinæmia, a properly constructed diet is of both symptomatic and general value. In chronic nephritis without œdema but with failure in renal concentrating power, there is much less satisfactory evidence that dietetic treatment will delay to any considerable degree the final onset of uræmia.

Principles of dietetic treatment in nephritis

To achieve the objects mentioned in the preceding section, the diet must be modified in some or all of the following important factors :—

1. The protein content.
2. The salt content.
3. The acid-forming or base-forming qualities.
4. The water balance.

1. **The protein content.**—There is no satisfactory evidence that a high intake of 100 to 200 g. of protein daily has any deleterious effect on a healthy kidney (Chapter 5). The effect of the protein intake on a diseased kidney is much more difficult to assess.

Formerly it was the practice to restrict the protein intake in all types of nephritis. This is certainly irrational. Indeed when proteinuria is excessive, there is a fall in the level of serum albumin and other evidence of protein deficiency (p. 74). Proteinuria *per se* is therefore an indication not for protein restriction but rather for a liberal intake to replace this waste. A high protein intake, when used to counteract hypoproteinæmia, has never been shown to have any deleterious effect on renal function. On the other hand, diets low in protein tend to produce anæmia and to lower vitality and resistance to infection. The personal experience of S. D. more than 40 years ago shows the ill-effects that can arise from protein restriction.

He had a kidney removed for hydronephrosis at the age of 12. Despite this handicap he managed to enlist in the infantry in August 1914 and spent the autumn, winter and spring in the trenches in Northern France under the dreadful conditions of wet and cold that existed during that period of the First World War. In the summer of 1915 he was very severely wounded and developed extensive gas gangrene. His life was seriously endangered from toxæmia, sepsis and cachexia for nearly a year. That his remaining kidney was markedly affected was manifested by the constant passage of albumin, leucocytes and casts in the urine. The diet prescribed and eaten for more than a year after discharge from hospital was low in protein and high in carbohydrate, and alcohol was prohibited. As the albuminuria continued and health was not fully restored, and because the restriction of food and drink proved extremely irksome, he decided to stop all dietary restriction and eat and drink whatever he liked. More than 40 years have elapsed since that decision and the function of the one remaining kidney appears to be perfectly satisfactory, as judged by the sense of well-being and the absence of abnormal constituents in the urine and the blood.

Nevertheless there is justification for some reduction of the protein intake when, as in chronic nephritis, there is impairment of the efficiency of the kidney in excreting the nitrogenous end-products of protein metabolism. Excretion of urea demands the expenditure of energy and oxygen by the kidney ; when the excreting mechanism is damaged, it seems logical to rest it. Protein restriction is also indicated in acute nephritis, on the grounds that reduction of the kidney's work to a minimum will rest the organ and so aid recovery.

Drastic reduction, however, is unnecessary for it is impossible to eliminate protein metabolism by excluding protein from the diet. The ' wear and tear ' of the body leads to a constant breakdown of protein—the endogenous protein metabolism. This amounts to between 20 and 40 g. of protein daily. It can be reduced to a minimum by giving a diet adequate in calories and in particular carbohydrate, which is well known to ' spare ' protein. There is no justification in acute nephritis for reducing the dietary intake of protein below the level of endogenous protein metabolism.

Most authorities believe that it is unwise to continue giving a diet containing only 20 g. of protein for more than a few days ; about 40 g. of protein daily are needed to meet the body's normal requirements. However, carefully controlled nitrogen-balance experiments, carried out by Olbrich (1944) under the direction of S. D., demonstrated that, while this is true of normal people, many nephritics with nitrogen retention are in negative nitrogen balance while in bed on a diet containing 2000 Cal. and 0·75 g. of protein/kg. body weight—*i.e.* 50 g. for a man of 65 kg. To continue in negative nitrogen balance invariably results in progressive loss of weight and strength. Accordingly we advocate that the protein intake should not be reduced below 50 to 60 g. daily, even when the blood urea is 100 mg./100 ml. or higher. When signs of impending uræmia appear, it may be advisable to reduce the intake of protein to 40 g. or less for a few days while fluids are being forced to increase diuresis. A return to a diet which maintains nitrogenous equilibrium must be made, otherwise the patient will die from inanition and malnutrition. When the output of urine finally decreases to a level which is not sufficient to clear the blood of products of protein metabolism, the patient's end is approaching and it is neither helpful nor kind to prohibit any reasonable demands he may make.

A common fallacy is that ' red ' meat is more harmful to patients with nephritis than ' white ' meat. Actually, red and white meats have a similar content of purines and extractives, and as only the end-products of protein metabolism reach the kidneys, it is of little importance whence these end-products were originally derived. When protein restriction is necessary the protein in the diet should be of the highest biological value as obtained from meat, fish, eggs and dairy products.

2. **The salt content.**—Œdema is always associated with retention of sodium and chloride ions as well as water. There is no doubt that the

degree of œdema in nephritis may be altered by varying the intake of salt. Yet other factors also determine the presence of œdema in nephritis.

(*a*) *Increased permeability of the capillary walls* may allow proteins as well as salts to pass from the plasma into the tissue spaces. This is a possible cause of the œdema of acute nephritis; the increased capillary permeability may be caused by the same toxic agent which damages the glomerular capillaries.

(*b*) *A fall in the colloid osmotic pressure of the plasma* follows a fall in the level of the plasma proteins (chiefly in the albumin fraction), due either to losses in the urine or to defective synthesis by the liver. In the capillaries, the osmotic pressure of the plasma proteins normally counteracts the hydrostatic pressure which is tending to force fluid outwards through the capillary walls. When the plasma protein falls from the normal 6 to 8 g./100 ml. to a level below 5 g./100 ml., the capillary blood pressure is no longer adequately opposed, and so fluid passes from the capillaries into the tissues.

(*c*) *Increased blood pressure within the capillaries* occurs in the chronic venous congestion of cardiac failure. The œdema found in chronic nephritis with hypertension is frequently cardiac in origin.

Retention of sodium is not the primary cause of any of the types of œdema seen in renal disease, yet the ingestion of salt will aggravate œdema due to any of the three factors mentioned above; hence the restriction of salt in the diet is indicated in nephritis with œdema. However, there is no justification for indiscriminate reduction in salt intake in all forms of nephritis. In chronic nephritis with hypertension but no œdema, salt restriction is not required unless cardiac failure supervenes, and it may be actually harmful by producing lack of appetite and consequent undernutrition.

The indications for restricting the salt intake in diseases of the kidney are given later in this chapter. The dietary means for effecting these restrictions and the difficulties involved have been discussed in Chapter 40, page 570.

3. **Acid-forming or base-forming properties.**—Besides regulating the osmotic pressure of the body fluids, the kidneys also maintain the *p*H of these fluids (Chapter 10).

Good results have been claimed for the treatment of nephritis by the use of diets which give rise to an alkaline urine. Such diets must be rich in fruit and vegetables and poor in meat, fish and eggs. A marked restriction of the latter foods makes the diet unappetising and monotonous. The prescription of alkalis (*e.g.* sodium citrate or bicarbonate, 4 g. t.d.s.) is a simpler and more effective method of making the urine alkaline. The acid-forming and base-forming properties of the diet have been unduly emphasised in the past (p. 149).

4. **The water balance.**—In nephritis with œdema, the output of urine is decreased. This may be evidence of impaired renal function, as in acute nephritis, or due to the deviation of water to œdema fluid by any

of the causes mentioned on page 577. Whichever of these causes is operative, the ingestion of large amounts of water will aggravate the œdema. Therefore restriction of the fluid intake is as important as salt restriction in the treatment of nephritic œdema. When œdema is present, the logical procedure is to reduce the fluid intake to a level below that of the fluid lost from the body, so that the œdema may be reduced. In Chapter 10 it was shown that the fluid intake from ' solid ' food plus the metabolic water formed in the oxidation of the food was approximately equal to the water lost from the lungs and skin. Therefore, to achieve a negative water balance, an attempt should be made in œdematous patients to keep the amount of fluid drunk below the urinary output. In extreme oliguria, such as occurs in many patients with acute nephritis, this is impossible. In practice it is found that a daily fluid intake of below 500 ml. cannot usually be tolerated for more than 2 or 3 days. Excessive fluid restriction leads to weakness, anorexia and irritability. As long as there is œdema, the fluid intake should, however, be restricted to not more than 1 *l.* daily.

Rigid fluid restriction in nephritis with œdema should only be practised when renal function, as judged by the concentrating power of the kidney, is good or shows only moderate impairment. Where the concentrating power is markedly diminished there is a possibility of uræmia supervening, which may be precipitated by fluid restriction. The kidney can only excrete waste products in dilute solution, and therefore if the intake of fluid is much reduced it may be insufficient to secure adequate elimination of waste products. In such cases, although œdema may persist and even increase, a more liberal fluid intake must be allowed.

In nephritis without œdema, there is no indication for fluid restriction and the fluid intake may be left to the patient's own desire.

DIET IN DIFFERENT TYPES OF RENAL DISEASE

The aims of dietetic treatment are not identical in the different types or stages of nephritis, so that it is essential to have a simple working classification of the different forms of nephritis. Dietetic treatment is largely symptomatic, and so is regulated by the degree of renal damage rather than by the precise pathological condition producing this damage ; the differentiation of the clinical types of nephritis is based largely on the predominant symptoms and the state of renal function. The following classification of nephritis will be used :—

***A.* Acute nephritis**

1. Acute glomerulonephritis (Type I nephritis, Ellis).
2. Acute focal nephritis.

***B.* Membranous glomerulonephritis (Type II nephritis, Ellis, hydræmic nephritis)**

C. Chronic uræmia (chronic renal failure without œdema but with hypertension and retention of nitrogen)

1. Terminal stage of acute glomerulonephritis (Type I nephritis, Ellis).
2. Terminal stage of membranous glomerulonephritis (Type II nephritis, Ellis).
3. Terminal stage of bilateral pyelonephritis.
4. Terminal stage of bilateral nephrosis.
5. Terminal stage of essential hypertension and nephrosclerosis.

D. Acute uræmia and tubular necrosis

Nephrotic syndrome.—This term is used to describe the clinical state of œdema associated with marked proteinuria and reduced plasma protein concentration. Type II nephritis is only one example of the nephrotic syndrome. Other disorders with renal involvement which give a similar clinical picture are amyloid disease, diabetes mellitus (Kimmelstiel-Wilson syndrome), poisoning by drugs, *e.g.* mercury, gold and troxidone, and compression or occlusion of the renal veins by enlarged para-aortic lymph nodes, by thrombosis or by renal carcinoma.

When terminal renal failure develops in the nephrotic syndrome, the proteinuria and œdema diminish. There are several explanations for these changes, but the most acceptable is that progressive fibrosis leads to a cutting off of the blood supply to the damaged glomeruli and tubules. In consequence, the leaking glomerular filters gradually disappear, with a reduction in the loss of protein in the urine. As a result, the level of the plasma protein rises. Another effect of the fibrosis and destruction of nephrons is a reduction in the power of the kidney to concentrate nitrogenous waste products. The kidney secretes large amounts of dilute urine which maintains the excretion of these products The combination of polyuria and the increase of the plasma protein explains the progressive disappearance of the œdema. At the same time signs of renal failure appear, *e.g.* urine of low and fixed specific gravity and a rise in the blood urea.

A. ACUTE NEPHRITIS

1. Acute glomerulonephritis (Type I nephritis, Ellis)

This disease occurs most commonly in children and young adults, the onset frequently occurring 1 to 3 weeks after a streptococcal infection, usually tonsillitis or scarlet fever. There is generalised toxic damage to the glomeruli and, to a lesser extent, to the tubules. Characteristically, there is a diminished output of urine, which contains albumin, blood and casts. Œdema of varying degree and a raised blood pressure are also present. Mild forms of the disease may show little general upset, and the œdema and hypertension may be transient or even absent ; in severe cases the patient complains of headache and nausea, and vomiting, hypertension and œdema are marked ; there is considerable nitrogen retention. In progressive cases a diffuse fibrosis develops which results in the destruction of many nephrons.

Treatment.—Complete recovery occurs in the great majority of patients ; hence the difficulty of assessing the value of any therapeutic measures. These consist of :—

REST AND WARMTH.—The patient should be kept warm in bed and protected from cold and draughts until hæmaturia, proteinuria, hypertension and œdema have disappeared. This will vary according to the severity of the condition from a few days to several months.

CHEMOTHERAPY.—Penicillin should be given for a week with the object of eliminating residual streptococcal infection of the tonsils and pharynx.

DIETETIC TREATMENT.—The aims are :—

Reduction of the protein intake.—On the basis of resting an inflamed organ, protein intake should be reduced to the level of the endogenous metabolism. This will lessen the work of the kidneys whose capacity to excrete the end-products of protein metabolism is impaired.

A low salt intake.—In acute nephritis there is a generalised increase in capillary permeability, and hence œdema. It is therefore rational to reduce the sodium intake so that the œdema should not be aggravated.

Restriction of the fluid intake.—This is also necessary to combat the formation of œdema fluid.

The dietetic treatment in severe and mild cases may conveniently be considered separately.

(*a*) SEVERE CASES.—The patient will be unable to take more than a light fluid diet and as the output of urine will be small, the fluid intake must be restricted. A maximum intake of 2 pints (1 *l.*) should be allowed or 1 pint (0·5 *l.*) plus an amount of fluid equal to the volume of urine passed in the previous 24 hours. Half of the fluid allowance can be given in the form of milk and 1 pint (0·5 *l.*) of milk provides a little less than 20 g. of protein. This will meet the larger part of the endogenous protein metabolism. Milk is usually tolerated well. As already explained there is no point in reducing the protein intake further as this will not reduce the amount of nitrogen which has to be excreted. The other half of the fluid intake can be given as 1 pint (0·5 *l.*) of 20 per cent. glucose or lactose with fruit juice or other flavouring agents.

Formerly, fruit juice was strongly recommended and a daily intake of 1 pint (0·5 *l.*) of fresh juice (sixteen oranges) was prescribed. In some recent books fruit juice is rigidly excluded from the diet. The reason for this change is the realisation that fruit juices contain considerable amounts of potassium and so could lead to potassium intoxication. Undiluted fruit juices may have a potassium content of up to 5 mEq./100 ml. Accordingly a daily intake of 500 ml. of orange juice might contain 25 mEq. (about 1 g.) of potassium, which might possibly be harmful to an anuric patient. A *via media* is sensible. Fruit juices may safely be used for flavouring drinks, but the large quantities previously advocated are probably best avoided.

The daily fluid allowance can be given in six drinks of equal size at approximately 4-hourly intervals, milk alternating with the glucose drink.

Except in rare cases which progress rapidly to anuria and renal failure and which should be treated on the lines recommended for acute uræmia (p. 587), the blood pressure falls, diuresis sets in, and the œdema disappears after a few days. When this occurs, the patient should be placed on a diet nearer to his basal protein and caloric requirements. Even if there is no apparent improvement, it is unwise to continue the milk and glucose diet for more than 7 to 10 days. The next diet should therefore contain approximately 45 g. of protein and about 1700 Cal. The protein quota is derived from dairy products (milk and eggs) and from cereals and vegetables. Diet No. 16 is suitable. Almost 50 per cent. of the protein of the diet is of high biological value, so that nitrogenous equilibrium should be assured.

Salt should not be used in cooking, and none should be added after the food comes to the table. The intake of fluids as such should still be restricted according to the urine volume.

Further additions to the diet depend on improvement in renal function tests applied at weekly intervals, the concentration test described on page 574 being the easiest and most satisfactory for repeated use. When the specific gravity reaches 1·018, and the level of the blood urea has returned to normal, the protein intake should be increased to about 60 g. by the addition of a good serving of lean meat, chicken or fish at one of the meals. If, however, after 2 or 3 weeks on 45 g. protein (Diet No. 16), no improvement in renal function has occurred, and particularly if the patient is losing weight and strength, it must be assumed that nitrogenous equilibrium is not being secured, and protein should be increased to 60 g. Progress towards normal renal function, as shown by the specific gravity of the urine reaching or exceeding 1·020, is an indication for a further increase in protein towards normal levels by a gradually increased intake of milk, eggs, cheese, meat or fish.

These generous protein allowances help rather than hinder the restoration of normal renal function, and certainly aid general recovery. The persistence of proteinuria is not an indication for modifying these dietetic measures, provided that the concentrating power of the kidney is not markedly impaired. As mentioned earlier, albumin in the urine represents protein lost to the body, and is an indication for a generous rather than a restricted protein intake to make good this waste.

(*b*) MILD CASES, with little general disturbance, hypertension, œdema or nitrogen retention in the blood, do not require the initial ‘ starvation ’ period, as they can tolerate a diet supplying their minimal protein requirements from the start. Such patients should be given at once Diet No. 16, and further additions should then be made according to the results of renal function tests, as described under the treatment of severe cases. When anæmia is present, iron in full doses is of great value.

2. Acute focal nephritis

This condition may occur in the course of various infections, chiefly those of streptococcal origin, especially tonsillitis. It usually develops at the height of the infection, and is characterised by the appearance of blood, protein and casts in the urine. There is no œdema or hypertension, however, and renal function is unimpaired. Focal nephritis is an incident in the casual infection, and has no effect on the prognosis, although it is more apt to occur in severe infections.

The treatment of focal nephritis is that of the primary infection. The renal complication does not require the dietetic measures used in acute diffuse nephritis to be so strict or so prolonged. It is usual to give a low protein diet until the hæmaturia and proteinuria have subsided, and Diet No. 15 is suitable. No fluid restriction is necessary. Within a week or two the hæmaturia and albuminuria will have disappeared, and a normal diet can be resumed.

B. MEMBRANOUS GLOMERULONEPHRITIS (TYPE II NEPHRITIS, ELLIS, HYDRÆMIC NEPHRITIS)

In the great majority of cases this condition develops insidiously, with no history of a previous acute attack. Occasionally it follows an attack of acute nephritis. The essential pathological lesion is a thickening of the glomerular walls and the capillary basement membrane in the glomeruli, which leads to a hyalinisation of the tufts. These specific changes have recently been demonstrated by electron microscopy and explain the reason why the term ‘ membranous glomerulonephritis ’ is used to describe this particular type of renal disease.

Membranous glomerulonephritis is characterised by :—

1. Marked œdema, oliguria and a heavy proteinuria.
2. Decrease in the plasma proteins, especially in the albumin fraction.
3. Increase in the plasma cholesterol.
4. Absence of cardiovascular changes.
5. Absence of impaired renal function and nitrogen retention.

In the early stages at least.

Treatment is directed chiefly towards relief of the œdema and under-nutrition consequent upon the loss of protein in the urine. For these purposes steroid therapy is a valuable aid. Arneil (1961) reviewing the records of 164 children with nephrosis treated since 1929, found that after its introduction 75 per cent. of the children eventually lost their œdema, the urine became free of protein and their blood chemistry returned to normal. The initial dose recommended is 60 to 80 mg. of prednisolone daily, which is gradually reduced to 10 to 20 mg. Treatment may have to be continued for many weeks or even months. In adults the response to steroids is much less satisfactory.

While awaiting the effect of steroid therapy, and for those patients who do not respond to this form of treatment, the following measures are indicated.

1. *Adequate protein intake.*—So long as renal concentrating power is normal, hypertension absent, and the blood urea not elevated, a liberal intake of protein is desirable in an attempt to make good the urinary loss of protein. At least 90 to 100 g. protein per day should be given. If this is not successful in reducing œdema, 150 g. or more should be tried for a few weeks, though many patients find it difficult or impossible to tolerate such a diet.

2. *Restricted fluid intake.*—This, along with salt restriction, is recommended to combat the marked tendency to œdema formation resulting from the fall in the plasma proteins. The intake of fluids as such should be restricted to about 1 to 1½ *l.* daily.

3. *Restricted salt intake.*—No table salt is permitted ; salt used in cooking must be reduced to a minimum. Sodium-rich foods such as ham, bacon, sausages, all tinned meats and fish, shellfish and cheese must be avoided.

Provided there is no failure in renal concentrating power, Diet No. 17 is suitable ; it contains about 100 g. of protein ; a restricted salt intake is necessary.

In addition to these dietetic measures for relieving œdema, diuretics may be of considerable value. Chlorothiazide is safer than mersalyl (an organic mercury preparation), is equally effective and has the advantage that it can be given orally. A supplement of potassium should always be given concurrently.

If the œdema is not relieved by the above treatment, then more vigorous measures must be tried. A *low sodium diet* with a high protein content should be given. For this purpose Diet No. 14 is recommended, with the protein intake increased to 120 g. This may be done by giving 60 g. of a casein preparation, such as Casilan (Glaxo) or Lonalac (Mead Johnson), which is practically salt-free. Should this fail the very high protein diet originally used by Epstein containing 150 g. of protein may be tried. To achieve this level 90 g. of a casein preparation would have to be given daily as a supplement to the *low sodium diet.* Casilan or Lonalac may be taken dissolved in water and given medicinally. Some of it may be incorporated in sauces, stews or home-made biscuits. An even higher intake of protein, as much as 250 g., has been recommended, but this can seldom be tolerated. Fluid restrictions must be continued as before.

The plasma cholesterol level is usually raised in nephrosis and so diets low in fat have been prescribed. The same dietary measures that lower the plasma cholesterol associated with ischæmic heart disease, sometimes lower it in nephrosis ; there is as yet no evidence that this benefits the course of the disease.

The *low sodium diet* is very irksome for the patient. He should be encouraged to persist with it for 3 weeks. If improvement has taken place, he can revert to Diet No. 17 with a restricted salt intake. If there is no improvement on the low sodium diet (Diet No. 14) it is doubtful whether further persistence with a severe restriction in the intake of sodium is of any use. Other measures can be tried. The administration of cortisone, or better still prednisolone, daily for months or sometimes for years is valuable for some adults with the nephrotic syndrome, and for a much higher proportion of children. In such cases proteinuria diminishes, the concentration of plasma proteins increases and œdema diminishes or may disappear completely. The ultimate value of this therapy is still unknown. Transfusions of blood plasma or plasma substitutes such as 6 per cent. gum acacia or the polysaccharide, dextran, have also been used, but are seldom successful.

The general health must be maintained by ensuring an adequate intake of vitamins and iron, by removal of septic foci and by treatment of intercurrent infections.

After a period which may be measured in years, the degree of œdema and proteinuria usually diminishes and at the same time hypertension and renal failure develop. When the non-protein nitrogen in the blood begins to rise, the downhill course towards uræmia is rapid in most patients. Dietetic treatment presents the greatest difficulty as the measures suitable for the treatment of œdema which is still present (high protein, low salt diet and reduction of fluid) are contraindicated for the treatment of nitrogen retention and in fact they may precipitate uræmia. As long as œdema is a marked feature, sodium restriction for its relief should be continued, but the protein intake will have to be modified according to the degree of renal damage as revealed by renal function tests. In general it is undesirable to reduce the protein intake to below 50 to 60 g. daily. The former practice of reducing the intake of protein to 30 to 40 g. has been shown to result in malnutrition, anæmia or lowered resistance. The careful observations of Aldrich and Boyle (1933) on a group of children suffering from chronic nephritis with œdema, hypertension and nitrogen retention, clearly indicated the benefits which accrued when their diet was changed from one low in protein to one in which the protein intake was adequate. Not only was the general health of the children greatly improved, but no consistent deleterious effects were produced on the hypertension, proteinuria or nitrogen retention. The management of renal failure with nitrogen retention is discussed in the next section.

URÆMIA

The retention of abnormal amounts of urea in the blood in renal disorders was amongst the early discoveries resulting from the application of biochemical methods to the elucidation of disease in general and of renal disease in particular. The term ‘ uræmia ’ has been used for a long time to describe the clinical state which arises from renal failure with nitrogen retention. As renal function becomes impaired other biochemical changes occur. These include disturbances in acid-base equilibrium, and abnormalities in water and electrolyte balance. They are probably more responsible for the clinical features of uræmia than a high level of blood urea. In addition, renal failure is nearly always accompanied by arterial hypertension, and this fact complicates still further the clinical picture and renders difficult any attempt to ascribe symptoms and signs to their basic cause.

Impairment of renal function commonly results from disease affecting the renal parenchyma and this form of uræmia is called *renal uræmia.* The renal failure may be acute or chronic. A wide variety of conditions give rise to acute renal failure with structural renal damage and these include acute glomerulonephritis, acute severe pyelonephritis, acute exacerbations of chronic pyelonephritis, malignant hypertension, polyarteritis nodosa and eclampsia. Chronic renal failure arises as a result of diseases which destroy tissue more slowly, *e.g.* chronic nephritis and chronic pyelonephritis, bilateral hydronephrosis, polycystic disease, hypertension, diabetic nephropathy, amyloid infiltration, tuberculosis and conditions causing hypercalcæmia.

Acute uræmia occurs also in patients in whom initially there is no primary parenchymal renal disease, but in whom acute circulatory failure leads to sudden reduction in renal blood flow ; this reduces the capacity of the kidneys to perform their functions normally. This occurs in states associated with water and salt depletion, shock, hæmorrhage, etc. Since the origin of the uræmia is not directly related to renal disease, the term *extrarenal uræmia* has been applied to it. With appropriate treatment this type of uræmia is reversible and the prognosis is generally good. In a proportion of cases of extrarenal uræmia due to acute renal circulatory failure, renal ischæmia may be so severe and prolonged as to produce necrosis of the renal parenchyma. When the necrosis affects only the tubules the condition is called *acute tubular necrosis.* More rarely the whole of the renal cortex is involved, the glomeruli as well as the tubules becoming necrotic. This has been called *renal cortical necrosis.*

Impairment of renal function arises also in conditions in which there is obstruction to the renal tract, *e.g.* senile hypertrophy of the prostate. This type of uræmia is called *post-renal uræmia* and is described on page 589.

C. Chronic Uræmia (Chronic Renal Failure)

The clinical picture of chronic uræmia is indistinguishable in the terminal stages of all the renal diseases listed on page 578 ; the dietetic treatment is the same for all types when chronic uræmia is present. Chronic uræmia without œdema and of moderate severity has no typical symptoms, and may only be revealed when proteinuria is discovered during physical examination for some unrelated condition. The only other physical sign usually present is a raised blood pressure. Occasionally this feature may be absent if tubular absorption is seriously damaged with the production of a ‘ salt-losing ’ nephritis (p. 586).

Chronic renal failure due to the causes mentioned above is usually of long duration, and the severe dietary restriction formerly enforced probably harmed more patients than it helped, by interfering with nutrition and so affecting the general condition adversely. Nevertheless some reduction of the protein in the diet will lessen the work of the kidneys. A fall in the blood urea usually results, in contrast to a rise which may occur if the protein intake is not restricted.

The diet in chronic renal failure without œdema is essentially a normal one, except for the protein content which must be modified according to the degree of impairment of renal function.

Mild cases.—When the damage to the kidney is only slight, as indicated by a normal blood chemistry but a reduction in the maximal specific gravity of the urine to about 1·018, the patient should be allowed about 70 to 80 g. of protein daily. The only instruction which need be given to the patient is that he should limit his intake of meat or fish to a *small* helping at lunch and dinner. Ample fruit and vegetables should be taken to maintain an adequate supply of vitamins and minerals. The intake of milk should be about ½ pint (0·25 *l.*) daily.

Moderate cases.—The maximum specific gravity of the urine falls to about 1·016 and an increase in the blood urea is found. Some curtailment of protein is necessary, but it is strongly recommended that the intake of about 60 g. of protein should be maintained as long as possible. Diet No. 18 will meet this requirement.

Severe cases.—Severe renal damage, as shown by a maximum specific gravity of about 1·014 or less and a high blood urea, is widely accepted by many authorities as an indication to reduce the protein intake to approximately 40 g. or less daily (Diet No. 16). The inadvisability of prescribing such low protein diets for nephritics, except for short periods, has been fully discussed on page 575. In the absence of œdema, cardiac failure or severe arterial hypertension, salt restriction is contraindicated. Occasionally ‘ salt-losing ’ nephritis develops due to a failure of tubular reabsorption and the patient requires additional salt. Restriction of the fluid intake is strongly contraindicated. The concentrating power of the kidney is reduced so that more water must be excreted in getting rid of the waste products. Fluid restriction would, therefore, tend to aggravate nitrogen retention and precipitate uræmia. The patient should take at least 5 pints (2·5 *l.*) of fluid daily. If there is clinical evidence of loss of calcium such as in tetany, calcium gluconate, 1 g. (15 gr.) t.i.d., should be given by mouth. Temporary cessation of twitching can be produced by the intravenous injection of 10 ml. of a 10 per cent. solution of calcium gluconate.

Severe acidosis should be treated by the intravenous infusion of a mixture of one part of one-sixth M. sodium lactate and two parts of normal saline.

The long duration of the disease makes it essential that any dietary regime must be as little irksome as possible to the patient, whose general condition and sense of well-being are the main criteria by which the effects of treatment are to be judged. Rest, sedatives and reorganisation of the patient's activities are probably of greater importance than dietary treatment. It is usual to forbid the use of alcohol on the grounds that it is a renal irritant. This concept dates back to the time of Bright, but there is little evidence that alcohol in moderate quantities causes any harmful effects to the kidney. Since alcohol is very largely oxidised to carbon dioxide and water this is not surprising. We calculate that considerably less than 1 ml. of alcohol will be excreted by the kidneys over a period of 1 to 2 hours after the ingestion of one small whisky, a small bottle of beer, or a glass of claret. Mosenthal (1931) in his monograph on nephritis states that " alcohol does not damage the renal parenchyma. Taken in appropriate quantities it will serve to stimulate a waning appetite, will give taste to a monotonous low protein, high starch diet and will act as a food and a protein sparer." He concludes that it can, therefore, be prescribed in any form of nephritis. As already mentioned, one of the authors has never restricted his reasonable demands for alcohol, despite the fact that he has only one kidney which was severely damaged in 1915-16, and no harm has resulted. We do not wish to imply that any therapeutic benefit is obtained by prescribing alcohol for nephritis, but there is no need to prohibit *entirely* the use of alcohol to a chronic nephritic who enjoys his *occasional* glass of beer, wine or whisky, and who perhaps has not many years to live.

When obesity is associated with chronic nephritis, an effort should be made to reduce the weight gradually by the use of a diet moderately restricted in calories (*i.e.* 1200 to 1500 Cal.).

Œdema occurring at this stage of nephritis is usually cardiac in origin, and should be treated accordingly, with the proviso that rigid fluid restriction must be avoided.

In all forms of chronic nephritis anæmia tends to develop for reasons which are not fully understood. In uncomplicated cases hæmatopoiesis is normoblastic in character and the anæmia, which is usually moderate in degree, is normochromic and normocytic. The response to all hæmatinics, including iron, is poor.

D. ACUTE URÆMIA (EXTRARENAL URÆMIA AND ACUTE TUBULAR NECROSIS)

It is vitally important to understand the mechanisms which lead to the production of extrarenal uræmia (p. 585) and to realise that, in contradistinction to chronic uræmia, they can often be prevented if proper treatment of the underlying cause is given in time. When progression to acute tubular necrosis has already occurred, life can frequently be saved by the measures described below.

Treatment

1. **Causal condition.**—With a view to preventing or minimising the renal lesion, the underlying cause should be treated urgently by the

administration of blood, plasma, glucose or other repair solution. Appropriate treatment must also be given for injuries, burns and other surgical causes and for infection. Dimercaprol (BAL) should be injected in cases of heavy metal poisoning.

2. **Oliguria or anuria.**—Clinical and pathological investigations have shown that although filtration through the glomeruli is much reduced and necrotic lesions are present in the tubules, recovery may take place provided the patient can be kept alive for a period which may be several weeks according to the severity of the renal damage. During this period every attempt must be made to reduce protein metabolism to the minimum, by giving no protein orally or parenterally and by reducing endogenous protein metabolism to the lowest possible level. A daily intake of 100 g. of glucose or lactose has a marked protein-sparing effect. If up to 300 g. of sugar can be given the remainder will help to reduce the inevitable loss in weight which occurs during the anuric phase. The sugar is given in solution in about 600 ml. of water which is administered daily by mouth or through an intragastric drip, if coma or vomiting is present. This amount of water will roughly meet the daily obligatory loss of water through the skin and lungs. If œdema or pulmonary crepitations appear, the intake of water must be reduced. If small amounts of urine are passed, these must be measured and a volume of half normal saline, equal to the volume of urine passed, is added to the glucose solution, provided there is no œdema. In febrile patients an extra allowance of water is required to replace fluid lost through visible perspiration. If persistent vomiting or diarrhœa occurs, the water and salt depletion should be treated by isotonic saline and by the appropriate amount of M/6 sodium lactate (p. 689). The latter is indicated only if the carbon dioxide content of the blood is significantly reduced. Supplements of ascorbic acid and vitamin B_1 are also added.

In many patients this treatment prevents the blood urea from rising more than 20 mg. per 100 ml. per day, and the accumulation of potassium from protein catabolism is usually not sufficient to have serious consequences.

Anabolic hormones (p. 74) have been widely used in the treatment of acute uræmia. There is no doubt that in some anuric patients their use has been followed by a marked decline in the rate at which the blood urea was rising (Blagg *et al.*, 1962). This can be presumed to be due to a reduced breakdown of tissue protein. This effect is uncertain and perhaps dependent on the presence of a satisfactory labile store of protein in the tissues. Their clinical value is not yet established.

In some patients, however, and especially in those suffering from severe infection or massive tissue damage, or in whom blood has become loculated in one of the tissue spaces, the rate of rise of blood urea and potassium is much more rapid and life is threatened with a few days. The conservative measures already described are then insufficient and the patient should be transferred to a centre equipped with means for extracorporeal dialysis (artificial kidney). By this means patients have been kept alive for long periods and have ultimately recovered, who previously would certainly have died. If patients are kept on a protein-free diet for more than 15 days, they may become severely malnourished, depending in part on their nutritional reserves. When extracorporeal dialysis is being used over a long period some dietary protein is probably advisable. An egg and milk mixture (½ pint milk and 2 eggs) will provide 30 g. of protein. Such a mixture should be given in divided doses and at the same time as the glucose. The protein-sparing action of glucose is greatest if the mixture and the glucose are given simultaneously.

It has been shown that the above therapeutic regime when speedily and efficiently carried out has greatly reduced the mortality from acute uræmia.

This protein-free regime is continued until signs of recovery appear and diuresis sets in. The patient can then be given a low protein diet containing about 45 g. of protein and sufficient fluid to replace the loss of water in the urine. Diet No. 16 will meet these requirements. The fluid intake should be determined by the volume of the previous day's urine. During this phase loss of potassium in the urine may be considerable and must be made good by the administration of fruit juice which is a rich source of potassium or by a daily supplement of potassium chloride by mouth. With further improvement in renal function a gradual return to a normal diet is made.

POST-RENAL URÆMIA

Uræmia may result from obstruction at any point in the urinary tract, *e.g.* in the ureters by calculi or at the outlet of the bladder by an enlarged prostate gland or in the urethra from stricture. Obstruction is sooner or later followed by infection (see below) and uræmia. This may be severe. Surgical treatment for the relief of the obstruction is essential. Provided this treatment has not been too long delayed, a good recovery may be anticipated.

DIET IN DISEASES OF THE URINARY TRACT REQUIRING SURGERY

Before operation, patients with impaired renal function should be given a diet rich in carbohydrate and with the amount of protein necessary to maintain nitrogen equilibrium, namely about 45 g. (Diet No. 16). After operation, this diet should be continued until renal function tests show that recovery from the kidney damage is occurring. The protein intake can then be raised to 60 g. daily (Diet No. 18), and with further improvement a normal diet can be taken.

DIET IN INFECTIONS OF THE URINARY TRACT

In contrast to nephritis, in which regulation of the diet forms a mainstay of treatment, infections of the urinary tract must be dealt with by chemotherapeutic agents and antibiotics and by relief of obstruction in the urinary tract. Dietetic treatment is of subsidiary importance. Nevertheless there are a few points in which attention to the diet may aid the other measures employed.

Acute pyelonephritis (acute pyelitis)

The infection is combated in the acute stages by promoting adequate drainage through an increase in the fluid intake, by changing the reaction of the urine so that it is unfavourable to the growth of the infecting organism, and by the use of suitable antibiotics or chemotherapeutic agents.

During the febrile stage of the illness the patient must be confined to bed. A light invalid diet is given, for example the semi-fluid diet No. 2. Thereafter a normal diet is allowed with no restriction of protein, as renal function is not impaired in the acute stage.

In order to increase the urinary output so that the urinary passages may be flushed out mechanically, the patient must increase his intake of fluids to at least 6 pints (3 *l.*) daily in the form of water, barley water, fruit drinks and weak tea. The organisms most commonly found in acute cystitis or pyelitis belong to the coliform group of bacilli, which flourish in an acid urine, and the reaction of the urine should be made alkaline by the use of the citrate, acetate or bicarbonate of sodium. Chemotherapeutic agents and antibiotics have revolutionised the treatment of infections of the urinary tract.

Chronic pyelonephritis (chronic pyelitis)

Every patient with pyelitis who fails to clear up completely with the measures described above requires a careful medical and urological examination. This is of vital importance because chronic pyelonephritis commonly leads to renal failure and uræmia. Genito-urinary tuberculosis, stone, or obstructive lesions, acquired or congenital, may be present and will require appropriate treatment before the control of pyuria can be accomplished. Anæmia, sepsis and constipation should be corrected. Plenty of fluids should be drunk.

In many cases in which the causal condition cannot be discovered or is irremediable, a suitable antibiotic such as sulphamethoxypyridazine or nitrofurantoin may be taken intermittently over long periods without harm to the patient and with beneficial bacteriostatic effects on the urine. Eventually over a period of years hypertension and renal failure develop in those cases in which the infection has never been eradicated. Dietetic treatment on the lines for chronic renal failure will be required.

In some cases of chronic pyelonephritis the tubules are damaged to an even greater extent than the glomeruli and hence signs of interference with tubular reabsorption may be superimposed on those of chronic renal failure. Of particular importance may be the occurrence of excessive loss of sodium chloride in the urine which causes weakness, anorexia, vomiting and a fall in blood pressure. Much more rarely excessive loss of potassium occurs leading to marked weakness or even paralysis. The clinical diagnosis should be confirmed by biochemical estimations of the serum sodium and potassium. Treatment of such cases of ' salt-losing ' nephritis consists of giving supplements of sodium chloride or potassium chloride by mouth in suitable amounts.

RENAL AND VESICAL CALCULI AND NEPHROCALCINOSIS

Urinary stones present problems which have fascinated doctors and chemists for generations and which are still largely unsolved. It has been suggested that dietary factors are responsible, at least in part, for the formation of stones and also that certain dietary restrictions may reduce the likelihood of their formation in susceptible persons. Here we can only give a brief account of the subject, but two excellent monographs are available from which full details can be obtained (Joly, 1929 ; Butt, 1956).

THE CHEMISTRY OF CALCULUS FORMATION

Stones may consist of uric acid, urates, calcium oxalate, calcium carbonate, calcium phosphate and other material. Very rarely cystine stones are formed. Stones are seldom ' pure,' but usually a mixture of several substances. Uric acid and calcium oxalate are the commonest constituents. McGeown and Bull (1957) have written a useful review of the chemistry of calculus formation.

Perhaps the real question is not " Why do some people develop stones ? " but rather " Why do we not all have stones ? " Some of the constituents of urine are present in concentrations in excess of their maximum solubility in water. Calcium oxalate, for instance, is often present in urine in amounts three or four times in excess of its maximum concentration in water. It has been suggested that urine contains certain substances, *e.g.* mucoproteins, hyaluronic acid and corticoids, which, by forming complexes, keep otherwise insoluble salts in solution in the urine.

Citric acid is a substance which appears to have an important action in this respect. Citrate combines with those calcium ions which are free when a poorly soluble calcium salt is present in water, and so allows more free calcium ions to pass into solution. Shorr (1945) has claimed that " citric acid is not a waste product but a useful urinary constituent by virtue of its capacity to enhance calcium solubility." The daily excretion of citric acid by man varies greatly and is affected by hormones, vitamin D and other factors.

The metabolic processes that determine the urinary excretion of colloids and citric acid are little understood.

The acidity of the urine also affects the solubility of its constituents. Oxalates and phosphates are more soluble in acid than in alkaline urine.

HISTORICAL AND GEOGRAPHICAL CONSIDERATIONS

Both the history and the geography of renal and vesical calculi differ markedly ; so much so that they may be considered as separate diseases.

Renal calculus

In the medical and surgical wards of hospitals throughout the world patients are to be found suffering from renal colic with stones in the kidney or ureter. Accurate figures for the incidence of renal calculi in any country are not available. There is a general impression that they are more common in countries with a hot climate than in temperate regions. As far as can be gathered from old textbooks and senior physicians, there is no indication that the incidence has changed either in living memory or in the more remote past.

Vesical calculus

Whereas renal calculus is equally common in men and women, vesical calculus usually occurs either in boys, in young men or in old men (in whom it is generally associated with prostatic obstruction or other cause of urinary stagnation). Formerly it was common in young boys in Great Britain, but now it is very rare. A similar decline has taken place in the incidence in all the prosperous countries of Europe and North America.

Excruciating pain often led the sufferers to desperate measures. Relief by operation was sought long before the era of anæsthetics and aseptic surgery. Accredited surgeons fought shy of the risks of the operation. Indeed cutting for the stone was expressly forbidden in the earliest forms of the Hippocratic oath. In consequence many sufferers availed themselves of the services of ‘ stone-cutters ’ or lithotomists. These men flourished in Europe between 1500 and 1800. Their craft was often handed down from father to son as a closely guarded secret. Eight generations of the Collot family practised in France, and some by attendance on the King or his family acquired the title ‘ Royal Lithotomist.’ Many lithotomists travelled widely seeking patients or perhaps avoiding the relatives of their less fortunate patients. During the nineteenth century the incidence of stone in the bladder began to decline in Europe. It is now a *rare* disease (except in elderly men).

In most parts of the tropics stone in the bladder is also uncommon, but there are well-defined ‘ stone areas.’ These exist in Southern China, Thailand, West Pakistan, Persia and other countries. In such areas the visitor may find a surgeon who has a chest or cupboard full of a miscellaneous assortment of bladder stones of every variety of chemical composition.

One of us had the opportunity to visit such an area in the Ubon provinces of Thailand (Passmore, 1953). The surgeon-in-charge of the hospital at the capital of the province kindly gave access to his hospital records. During 4 years he had removed 610 bladder stones. This corresponded to a yearly rate of 1·8 operations per 10,000 inhabitants of the province, but this gives a false impression of the incidence. The disease, in fact, is largely confined to young boys. Between the ages of 4 and 6, the operation rate amongst boys was over ten per 10,000 boys. The relative immunity of young girls is probably attributable to their anatomy; it is easier for them to pass small stones *per urethram*. These operation rates do not reflect the whole incidence. During visits to villages in the neighbourhood, many children were found who had suffered from stones but who had managed to pass them. In some villages the incidence was very high and the symptoms of stone were well known.

ÆTIOLOGY

1. **Climate.**—A hot climate may be a contributory factor to the formation of both renal and vesical calculi. For if there is excessive loss of water in sweating, the urinary volume is likely to be diminished. The urinary constituents will then be more concentrated and so more likely to precipitate out. Climate can at most be a contributory factor, for renal calculus is still frequently encountered and vesical calculus was formerly very common in countries with a temperate climate.

2. **Occupation.**—In temperate climates some workers, *e.g.* stokers, boilermen and miners, may be exposed to high temperatures and so sweat excessively.

3. **Dietary factors:** (*a*) **Observations in man.**—The great fall in the incidence of vesical calculus among children and young adults in Great Britain coincided roughly with the marked improvement in the nutrition of the people: the disease predominantly affected the poorer classes. In all the ‘ stone areas ’ in Asia the diet is far from ideal and is generally of a poor vegetarian nature. These facts suggest a dietary cause for the disease.

Nevertheless there are other facts that are not consistent with this view. In former times prosperous men sometimes suffered from stone. Samuel Pepys was “ cut for the stone ” in 1658 when he was 25, and we know from his *Diary* that he lived well. In the “ stone areas ” of Thailand the nutritional state of the children is not good, when judged by modern European or American standards. Yet the children compare favourably with those in other parts of Asia, especially in many parts of rural Madras, where deficiency diseases are common, but stone in the bladder is rare.

(*b*) **Observations on experimental animals.**—McCarrison and others have produced both renal and vesical calculi in animals by dietary means. McCarrison concluded that “ there appeared to be two categories of dietetic factors concerned in stone formation : (*a*) positive factors, including excess of lime in the diet and some unknown agent present in whole cereal grains ; and (*b*) negative factors, including deficiency of vitamin A. . . ." The experimental diets used by McCarrison for the production of stone in animals had little resemblance to human diets and so his results must be interpreted with caution (Sinclair, 1953).

There is no conclusive evidence that dietary factors play any part in the ætiology of renal calculi. The diet may well be in some way responsible for vesical calculi, but these do not arise as a result of a simple deficiency of any known nutrient. McCarrison's concept of a combination of positive and negative factors being responsible for stone in the bladder in the tropics remains a useful working hypothesis.

4. **Sepsis of the urinary tract.**—Any chronic infection of the kidney or urine is liable to give rise to stones ; pus cells, dead bacteria and epithelial cells form a starting point around which a stone may form. However, the irritation and stagnation of urine, consequent upon the presence of a stone, frequently leads to infection. Hence in many patients it is impossible to tell whether the infection gave rise to the stone or *vice versa.*

5. **Stagnation of urine.**—This is a frequent cause of vesical calculi in old men and may be due to prostatic obstruction of the urinary flow or other disease of the urinary passages.

6. **Prolonged confinement to bed.**—This is a common cause of stone formation. Confinement to bed may lead to rapid decalcification of the bones and the calcium is then excreted in the urine.

7. **A raised level of calcium in the blood.**—This nearly always causes stone formation ; it is a characteristic feature of the rare disease, hyperparathyroidism, Cushing's syndrome, sarcoidosis and vitamin D intoxication (p. 205).

8. **Certain rare congenital biochemical abnormalities.**—(*a*) **Cystinuria.**—This is due to a failure of the renal tubules to absorb the amino acids, cystine, lysine, arginine and ornithine (Harris, 1957). Large amounts of these amino acids appear in the urine. Cystine is the least soluble and in consequence tends to precipitate out of the urine and form stones.

(*b*) **Primary hyperoxaluria** (Archer *et al.*, 1957).—In this condition there is an excessive metabolic formation of oxalate, probably by conversion from glycine. There is no evidence either of excessive absorption of oxalate from the alimentary tract or a failure of absorption by the renal tubules. The increased oxalate readily precipitates out and forms stones.

Both cystinuria and primary hyperoxaluria are very rare.

9. **Excessive excretion of uric acid,** *e.g.* gout and leukæmia.

10. **Unknown factors.**—In Great Britain and other prosperous countries, renal stones are frequently found to be associated with none of the above ætiological factors. They often arise in well-nourished young men who are otherwise fit and healthy. No obvious cause is found.

COMMENT.—Unfortunately all these observations leave the problem of the 'stone areas' in the tropics unsolved. Halstead (1961) sums up the situation admirably: "Whatever the ætiology of bladder stones in children in Thailand, the mechanisms of this disease should be amenable to further clarification by modern biochemical and epidemiological techniques. A concerted effort to solve the riddle might well begin in Thailand where the health of thousands of children is jeopardised by this capricious disease."

Clinical Features

These will vary according to the size, shape and position of the stone, and the presence and nature of the underlying condition. Renal calculi may be present for many years and yet give rise to no symptoms. The most common complaint is an intermittent dull pain in the loin or back, increased by movement or a sudden jolt. Some abnormal constituents of the urine, *e.g.* red cells, protein or pus cells, can be found at one time or another in most cases. When a stone is small enough to enter the ureter and large enough to obstruct it, an attack of renal colic develops. The patient is suddenly aware of intense pain in the loin, which soon radiates round the flank to the groin and often into the testis or labia in the sensory distribution of the first lumbar root.

Treatment

The immediate treatment of renal pain and renal colic is rest in bed, the application of warmth to the seat of pain and the giving of analgesic and antispasmodic drugs. Antibiotics are needed for the prevention and treatment of infections. In many cases the stone will pass *per urethram*, while the patient is on this regime. If the stone is not passed within a few days, an experienced urologist should be called in to investigate the case for the presence and site of the calculi and for anatomical and pathological lesions which may cause infection and urinary stagnation. He should decide if and when to operate. Suitable medical or surgical measures should be instituted for the correction of any primary cause of renal lithiasis that may have been discovered.

The next problem is the prevention of recurrence. Infections and anatomical abnormalities of the urinary tract must be appropriately treated, as these increase the liability to stone formation. There is no treatment for the underlying chemical disorders responsible for cystinuria and primary hyperoxaluria, which are fortunately very rare, other than insisting on a large fluid intake.

Since the constituents in renal and vesical calculi are all found in (or derived from) numerous articles of food, it is not surprising that physicians have frequently advised dietary restrictions of various kinds depending on the nature of the stone. These restrictions are aimed at reducing the output in the urine of relatively insoluble substances. Their value is now criticised on three grounds. First, the urinary output of oxalate, urate and phosphate, from which stones are usually formed, is now known to depend more on endogenous metabolism than on exogenous sources. Secondly, stones seldom consist of a single substance, and the dietary treatment of mixed stones obviously presents grave practical difficulties. Thirdly, the evidence that dietary restrictions are successful in the prevention of urinary calculi is unsatisfactory. For these reasons many authorities impose no dietary restrictions, since it is unlikely that they will be effective, and the treatment causes considerable inconvenience to the patient. This view is generally sound, but we feel that there are circumstances in which some dietary restriction may be advisable.

Calcium stones.—Hypercalcinuria is undoubtedly of importance in the causation of calculi. It occurs as a consequence of prolonged recumbency, a high intake of calcium as when large amounts of milk are consumed, hypervitaminosis, hyperparathyroidism, long-continued acidosis and—for no apparent reason—idiopathic hypercalcinuria. When any of these disorders is present, appropriate measures for its control must be undertaken. In addition, the intake of calcium should be reduced by limiting the consumption of calcium-rich foods, especially milk and cheese. Since acid urine increases the solubility of calcium phosphate and magnesium ammonium phosphate, an acidifying drug should be given, *e.g.* sodium acid phosphate, 3 g. daily.

TABLE, 41 1. *Oxalic acid content of foods*

Rich sources (100 to 500 mg./100 g.)	Moderate sources (25 to 100 mg./100 g.)	Poor sources (below 25 mg./100 g.)
Rhubarb Spinach Sorrel	Haricot beans Common beans Beetroot Dried figs Currants Prunes	All foods of animal origin Most foods of vegetable origin

Oxalate stones and oxaluria.—Usually 80 to 90 per cent. of the oxalate in the diet is not absorbed, but passed in the fæces as insoluble calcium salts. Urinary oxalates are mostly endogenous in origin. Absorption may be increased if the patient has hyperchlorhydria, since the excess acid may render the oxalates more soluble. Oxalates may also be produced by the action of intestinal bacteria from the fermentation of carbohydrate in the large bowel. Certain foods also are rich in oxalates, notably rhubarb and spinach (Table 41, 1). Tea, coffee and cocoa are also rich, but very small amounts of oxalates pass into the infusions. Tomatoes and strawberries contain little oxalate.

If a patient has passed a stone which is mostly oxalate, and if he continues to pass gravel, or urine with large numbers of oxalate crystals, and if pain and dysuria persist, it is wise to eliminate rhubarb and spinach from the diet. Restriction of other foods containing oxalates is only justified by a process of trial and error. If the ingestion of any such food is followed by dysuria and the passage of urine containing oxalate crystals and blood, then obviously this food must be avoided.

No dietary restrictions are necessary for people who have had an oxalate stone removed and are then free of symptoms, and whose urine contains only a few oxalate crystals.

Uric acid and urate stones.—The uric acid in the urine is derived in part from purine in nucleoproteins in the diet and in part from synthesis in the body (p. 121). The output in the urine is relatively independent of the nature of the diet. As Table 43, 1 (p. 642) shows, liver, kidney, sweetbreads, roe, sardines and sprats are the only foods rich in purine. These are the foods from which an excess urinary output of uric acid might be derived. It is advisable for anyone who has suffered from a stone composed predominantly of uric acid or urates, if he continues to pass gravel or have dysuria, to avoid all such foods. Though the effectiveness of these restrictions is uncertain, the advice is worth while, since little or no hardship is imposed by following it. Significant amounts of uric acid are not derived from tea, coffee or cocoa as normally consumed and no restriction of these beverages is needed. The maintenance of an alkaline urine by the administration of alkalis is of some value in keeping uric acid in solution.

Phosphates.—Phosphatic calculi are formed only in alkaline urine. When there is known to be a tendency for the formation of such stones, the urine should be kept acid with small doses of ammonium chloride. Owing to the wide distribution of phosphorus in foodstuffs, it is difficult to reduce its intake significantly.

The presence of a persistently alkaline urine strongly suggests a focus of infection requiring treatment.

Provision of an adequate fluid intake

This is by far the most important prophylaxis against recurrence of all forms of stone. A daily flow of urine of at least 4 pints (2 *l.*) will flush out the urinary passages and help to wash out particles of gravel. To achieve this at least 6 pints (3 *l.*) of fluid a day must be drunk.

If the climate or the patient's occupation cause much sweating, then the fluid intake will have to be greatly increased. Europeans who have suffered from renal colic should not be debarred from working in the tropics, but they must see that in all circumstances their fluid intake is sufficient to promote the urinary output recommended. Occasional measurements of urinary output by the patient may be a useful reminder to him of this necessity.

CHAPTER 42

DIABETES MELLITUS

WITH the exception of diabetes mellitus, few endocrine diseases have any direct association with nutritional failure, and few require any special dietetic treatment ; nevertheless the normal secretions of these glands depend ultimately on a proper dietary supply of the raw materials from which they are made. Many hormones are proteins or polypeptides, but because of their great importance to the body it is probable that their synthesis has priority over many other proteins when animo acids are in short supply.

The interrelationship between nutritional health and endocrine disorders is at best poorly defined and, so far as is known at present, can be little helped by dietetic treatment, except when the disorder is sometimes associated with *obesity* (*e.g.* Cushing's syndrome) or with *subnutrition* (*e.g.* in Addison's disease and sometimes in Simmonds' disease).

DEFINITION

Diabetes mellitus is a chronic disease due to deficiency or diminished effectiveness of insulin. The disease affects the metabolism of carbohydrates, proteins, fats, water and electrolytes—sometimes with grave consequences. The most obvious abnormality is a high level of glucose in the blood (hyperglycæmia) with consequent loss of glucose in the urine (glycosuria).

INCIDENCE

Diabetes is a common disease. Recently there have been several surveys recording its incidence. One of the most thorough has been by a group of 10 general practitioners in the city of Birmingham (College of Practitioners Working Party, 1962). Out of 19,412 patients, 18,552 had their urine tested. There were 119 known diabetics (0·64 per cent. of the population) and 127 new diabetics were discovered (0·69 per cent.). The total incidence of diabetes was thus 1·33 per cent. Similar figures have been obtained in other less extensive surveys both in North America and in Europe. It would appear that there are at least half a million diabetics in Great Britain, half of whom do not know that they have the disease. The disease is also common in the tropics, though much less is known about its incidence in underdeveloped countries. Tulloch (1962) has written a monograph on diabetes in the tropics.

ÆTIOLOGY

HEREDITY.—This is the most important single ætiological factor. In the Birmingham survey 26 per cent. of known diabetics had a close relative affected, as against only 7 per cent. of a control group. A recessive gene appears to predispose to the disease.

AGE.—Diabetes is a disease of the elderly ; in the Birmingham survey it was roughly eight times as common over the age of 50 as under. Probably the onset is after 40 in 75 per cent. of patients.

SEX.—The true sex incidence is about equal, but owing to the prominence of the symptom pruritus in females, the disease is more likely to be diagnosed in middle-aged or elderly women than in men.

OBESITY has for long been described as an important factor contributing to the onset of the disease. However, in the Birmingham survey, only 15·1 per cent. of newly diagnosed patients were classified as obese against 9·2 per cent. of a control group. This difference, though small, was statistically significant.

STRESS, either physical or emotional, often appears to be responsible for the onset of diabetes. Severe stress, such as a car smash, probably does not cause diabetes in people who would otherwise never have had it, but it may well be responsible in genetically predisposed people. Infections, in a similar way, are sometimes responsible for the onset in those predisposed to the disease.

CHEMICAL PATHOLOGY

The two predominant metabolic defects in diabetes mellitus are (1) the failure of the peripheral tissues to remove glucose from the blood fast enough, and (2) the release by the liver of excessive amounts of glucose into the blood ; the resultant underutilisation and overproduction of glucose causes the hyperglycæmia. Several factors may operate to produce these metabolic defects ; the extent to which they do so varies from case to case. Diabetes is not a single disease, but a syndrome that conceals several different pathological processes in a common clinical picture. In every case, however, it is fair to assume that the insulin secreted by the pancreas is either insufficient in amount or ineffective in action.

Mode of action of insulin.—When Banting and Best first discovered insulin in Macleod's laboratory in Toronto in 1922, diabetes seemed a simple problem—namely a defective production of insulin by the pancreas. However, the mode of action of insulin is still not fully understood. Two recent books have been devoted to this subject (Young, 1960 ; Krahl, 1961).

Insulin is certainly an anabolic hormone which facilitates the laying down of carbohydrate, protein and fat in the tissues. In this way it is essential for the normal utilisation of food by the body. Insulin assists the entry into the cells of glucose (certainly), amino acids (probably), and fatty acids (possibly). The exact way in which this is accomplished cannot as yet be stated in terms of physical chemistry.

Insulin lowers the blood sugar by encouraging the combustion of carbohydrate in the tissues, the deposition of glycogen in the muscles and liver, and the deposition of fat in the adipose tissues.

Causes of the biochemical lesion

1. DEFICIENCY OF INSULIN SECRETION.—The simplest explanation of hyperglycæmia in diabetes mellitus is a failure of insulin production by the β cells of the islets of Langerhans. In support of this explanation morbid histological changes can be demonstrated in the islets in the majority of long-standing cases examined at autopsy. In rare instances other pathological processes affecting the pancreas, such as carcinoma or hæmochromatosis, may give rise to diabetes.

2. DIMINISHED EFFECTIVENESS OF INSULIN.—Simple islet failure, however, cannot be the complete explanation in many cases. Even when the whole pancreas has been removed for the surgical treatment of malignancy, the insulin requirement of the patient thereafter seldom exceeds 40 units daily. Yet many diabetics need more than this; exceptionally as much as fifty times this dose may be required. Such cases of insulin resistance are due to factors opposing the action of insulin.

RESISTANCE TO INSULIN may originate in :—

Insulin antagonists. These can be demonstrated in the plasma of normal persons and, in greater quantities, in the plasma of most diabetics (Vallance-Owen, 1960; *Lancet*, 1961*b*). They are dialysable and possibly polypeptides. Their production appears to be dependent on the pituitary and adrenal glands. They can be shown to inhibit the action of insulin in accelerating the uptake of glucose by the isolated rat diaphragm muscle. Until more is known about the nature of these antagonists and the circumstances under which they are produced in the body, it is impossible to state how large a role they play in the ætiology of diabetes. The evidence available suggests that they are important.

The endocrine glands, which produce hormones known to antagonise insulin are as follows :—

The anterior pituitary gland.—The growth hormone (somatotrophin, SH) is diabetogenic; excessive production inhibits the action of insulin in the tissues. This presumably accounts for the diabetes that occurs in some giants or acromegalics with eosinophil adenomas of the anterior pituitary.

The adrenal cortex.—Hydrocortisone and other hormones with a cortisone-like action stimulate gluconeogenesis from protein (p. 74). The injection of cortisone, or increased cortical secretion under the influence of injected corticotrophin, converts protein to glucose. The result is an increased formation of glycogen and in some cases hyperglycæmia. Excessive production of glucocorticoids occurs in Cushing's syndrome and accounts for the appearance of mild, but insulin-resistant, diabetes in that disorder. Insufficient production of glucocorticoids occurs when the adrenal cortex or the anterior lobe of the pituitary gland is damaged. Hence patients with Addison's disease or Simmond's disease are extremely sensitive to injected insulin.

The pancreas.—The α cells of the islets of Langerhans produce a hormone (glucagon) which causes hyperglycæmia probably by increasing the breakdown of liver glycogen.

Consequences of hyperglycæmia

Glycosuria results if the glucose concentration in the blood rises to a level above the capacity of the renal tubules to reabsorb it from the glomerular filtrate. This level is known as ' the renal threshold.'

Polyuria.—The excess glucose in the glomerular filtrate hinders the reabsorption of water within the lumen of the renal tubule and so promotes an osmotic diuresis.

Water and electrolyte depletion result from polyuria unless sufficient fluid and salt are constantly being taken to replace the losses.

Effects on fat metabolism.—When fat combustion is proceeding to a disproportionate extent, aceto-acetic acid and its derivates β-hydroxybutyric acid and acetone begin to accumulate and appear in excessive amounts in the blood, producing ketosis (Chapter 9). As a consequence, acidosis may develop. This acidosis with associated dehydration can result in coma and even death.

The increase in fat catabolism (and consequent ketogenesis) that may occur in diabetes is probably accelerated by hormonal influences. Injections of growth hormone will raise the level of blood ketones in both man and experimental animals.

With the increased mobilisation of fat, the liver is often enlarged and fatty in diabetes. The serum may be milky (lipæmia) through excess of neutral fat and cholesterol.

Effects on protein metabolism.—The steady loss of glucose in the urine is often partly compensated by increased gluconeogenesis from the proteins of the tissues. The result is an increase in urinary nitrogen and wasting of muscles—an important clinical feature of severe diabetes.

Morbid anatomy

Histological examination of the pancreas *post mortem* reveals morbid changes in the islets of Langerhans in the majority of cases. The most common change is hyalinisation ; more rarely there is fibrosis or ' hydropic degeneration ' which has lately been shown to be due to infiltration with glycogen. In about a third of cases the islets appear normal by ordinary staining methods, but modern techniques have shown that in such cases there may be a numerical reduction in β cells relative to the number of α cells present. Otherwise the only pathognomonic appearances at autopsy are those due to secondary changes in the retinal vessels and renal glomeruli.

Clinical features

The presenting symptoms may be (*a*) polyuria due to the glycosuria. This may be particularly troublesome at night (nocturia) ; (*b*) dry mouth or thirst, due to dehydration ; (*c*) loss of weight and weakness due to loss of glucose in the urine and breakdown of tissue protein ; (*d*) pruritus vulvæ or balanitis due to local infection ; (*e*) pain in the legs at night ; (*f*) failing vision due to swelling of the lens consequent on osmotic changes secondary to hyperglycæmia ; (*g*) recurrent infections ; (*h*) amenorrhœa or impotence ; (*i*) coma.

In many mild diabetics the above clinical features may be insufficiently marked to attract attention or complaint ; in which case the disease is usually diagnosed when symptoms due to the development of one or other of the complications of diabetes cause the patient to seek medical advice, or when glycosuria is fortunately discovered during some other illness or at routine examination for life insurance. Diabetic retinopathy (p. 624) is of particular diagnostic importance because of its characteristic picture.

Unfortunately, it sometimes happens that patients with diabetes are never seen by a doctor until they are admitted to hospital in coma. Diabetes mellitus is therefore important in the differential diagnosis of the unconscious patient.

Diagnosis

This is made on the clinical features of the disease or, sometimes, on those of its complications, and is confirmed by the detection of glucose and perhaps ketone bodies in the urine. Benedict's test is the traditional method for detecting the sugar. It is now largely replaced by two modern alternatives : (*a*) ' Clinistix,' consisting of an impregnated paper stick which turns blue when dipped in urine containing glucose. No other urinary constituent gives this reaction ; it therefore provides a quick and specific qualitative test for glucose. (*b*) ' Clinitest ' tablets, which provide an easy, semi-quantitative method of testing urine for glucose. However, it is not entirely specific, since it also detects other less common reducing substances, including other sugars.

A patient who complains of some or all of the following symptoms—loss of weight, thirst, polyuria and pruritus vulvæ, has a dry tongue and whose urine contains glucose and ketone bodies, suffers from diabetes mellitus ; the diagnosis is definite. To determine the blood glucose in such a case may be an aid to subsequent treatment, but is unnecessary for the purpose of diagnosis.

Mild diabetes cannot be excluded on the basis of a normal fasting blood glucose or absence of glucose in the urine passed on rising in the morning. The diagnostic specimen of urine is the one passed 2 to 3 hours after the largest meal of the day.

Sometimes, however, in the course of a life insurance or army medical examination, or in a routine test in hospital, the urine is found to contain glucose in the absence of any admitted symptoms. It will then become necessary to decide, by a glucose tolerance test, whether the patient, in fact, has diabetes.

The glucose tolerance test.—The patient, having been on an unrestricted carbohydrate intake for several days, fasts overnight. In the morning he empties his bladder and has a sample of blood withdrawn to measure the fasting blood glucose level. He is given 50 g. glucose by mouth, dissolved in about 200 ml. of water. Thereafter blood and urine specimens are collected at half-hourly intervals for 2 hours, and their glucose content estimated. Venous or capillary blood can be used. The values for capillary blood glucose concentration are usually higher by 10 to 20 mg./100 ml. in the course of the test.

Using *capillary blood*, normal limits are set by the following three criteria :—

> The fasting blood glucose level does not exceed 120 mg./100 ml.
>
> Following the ingestion of the glucose, the blood glucose level does not rise above 180 mg./100 ml. (the usual renal threshold).
>
> The blood glucose has fallen to 120 mg./100 ml. or less within 2 to 2½ hours.

In addition no glucose should appear in the urine during the course of the test.

ABNORMAL GLUCOSE TOLERANCE TESTS.—If the response to the test is abnormal, as judged by failure to meet any *two* of the above *three* criteria, the diagnosis of diabetes can be made. Sometimes there is a failure to meet *one* criterion only. This happened in 36 per cent. of the persons found to have glycosuria in the Birmingham survey (p. 598). The most common of these abnormalities was a peak above 180 mg. either at half an hour or 1 hour, associated with a return to the normal level at 2 hours. This has been called ' lag-storage ' and may be due either to a failure of the liver and muscles to store glucose at the normal rate, or, more probably, to an excessive rate of absorption from the alimentary canal. *Alimentary glucosuria* is not uncommon in patients with duodenal ulcer or who have had a gastrectomy or gastro-enterostomy performed. Persons with single abnormalities of the glucose tolerance test usually do not have symptoms of diabetes and most people showing them remain fit and free from diabetes for many years, perhaps for life.

OTHER CAUSES OF GLYCOSURIA

Renal glycosuria. In some people with glycosuria (12 per cent. in the Birmingham survey), the blood glucose tolerance curve is normal, but glucose leaks into the urine at levels below 180 mg./100 ml. This is because they have a low renal threshold for glucose. During the war this was found to be the most common cause of glycosuria in young army recruits. Such people do not have diabetes and appear to have no increased liability to develop the disease subsequently.

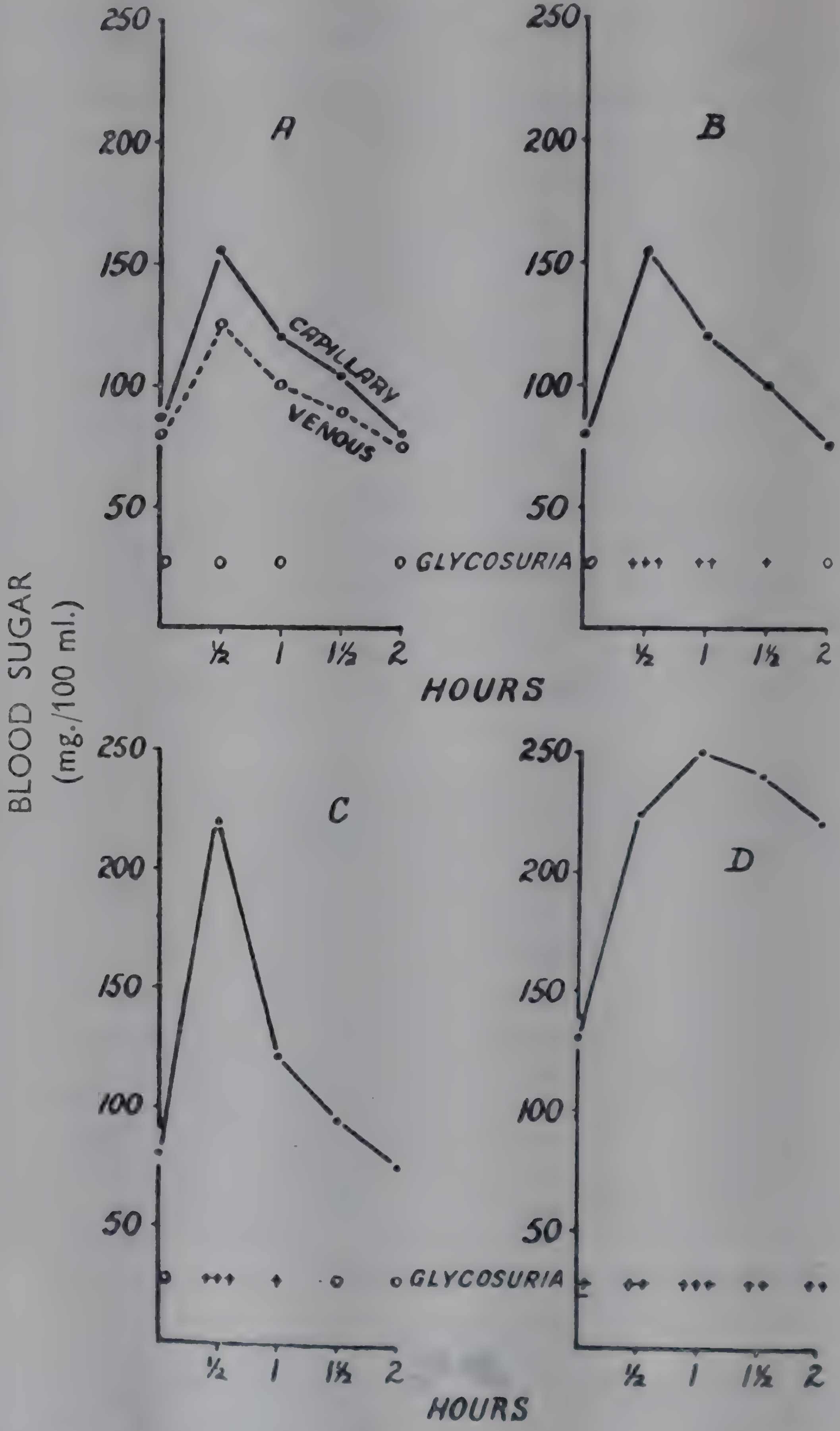

FIG. 42, 1

The glucose tolerance test. Blood glucose curves after 50 g. glucose by mouth, showing *A*, normal curve; *B*, renal glycosuria; *C*, 'lag storage'; and *D*, diabetes mellitus of moderate severity.

Miscellaneous causes

ALIMENTARY GLUCOSURIA (p. 603).

EMOTIONAL GLYCOSURIA.—Glucose is sometimes found in the urine of normal people in times of stress, *e.g.* before a race or an examination. This is attributed to the release of adrenaline from the adrenal medulla. Adrenaline mobilises liver and muscle glycogen and causes a transient elevation of blood glucose.

PREGNANCY GLYCOSURIA.—The renal threshold for glucose is sometimes lowered in pregnancy, resulting in renal glycosuria. Lactose occasionally appears in the urine towards the end of pregnancy.

RAISED INTRACRANIAL PRESSURE, *e.g.* from a cerebral vascular accident or tumour, may cause glycosuria.

SEVERE DAMAGE TO THE LIVER, *e.g.* in cirrhosis there may be defective storage of glycogen, with consequent hyperglycæmia and glycosuria following a carbohydrate meal.

OTHER ENDOCRINE DISORDERS.—In Cushing's syndrome and acromegaly, hyperglycæmia and glycosuria may occur, sometimes with sufficient severity to cause signs and symptoms of diabetes.

Hyperthyroidism and diabetes mellitus are not infrequently associated ; when this occurs, adequate control of the hyperthyroidism always reduces the severity of the diabetic state.

Other sugars appearing in the urine.—(1) Lactosuria, which is sometimes found late in pregnancy or during lactation, gives a positive reaction to 'Clinitest' but not to 'Clinistix' ; hence the latter is particularly useful in obstetric clinics.

(2) Pentosuria and fructosuria occur with extreme rarity as a result of inborn errors of metabolism (Chapter 44) or the ingestion of large amounts of fruit.

Detection of ketone bodies in urine.—The sodium nitroprusside test originally described by Rothera is a sensitive index of the presence of aceto-acetic acid (the parent ketone body). The reagents have been conveniently concentrated into Acetest tablets which have replaced the original Rothera test in clinical practice. Ketonuria may be found in normal people who have been fasting for long periods, repeatedly vomiting or eating a diet very high in fats and low in carbohydrate. Ketonuria is therefore not pathognomonic of diabetes, but if both ketonuria and glycosuria are found, the diagnosis of diabetes is practically certain.

TREATMENT

The aims of treatment are :—

1. The abolition of symptoms.
2. The correction of the hyperglycæmia and glycosuria.
3. The attainment and maintenance of satisfactory body weight.
4. The prevention of complications.

In practice, these aims are most likely to be achieved if the hyperglycæmia is properly controlled. With regular supervision diabetics can expect to live a reasonably normal life except for attention to diet and the injection of insulin if required.

Treatment requires the complete co-operation of the patient. As soon as the diagnosis is certain the patient should be told that he has diabetes ; at the same time he should be reassured, especially if a near relative has died of the disease. The new patient may gain confidence in the waiting-room of a diabetic clinic by talking to healthy diabetics who have been under medical supervision for years.

There are three methods of treatment :—

1. Diet alone.
2. Diet and insulin.
3. Diet and oral hypoglycæmic drugs.

When a diabetic is seen for the first time it must be decided whether or not the diabetes is sufficiently severe to require immediate treatment with insulin. If not, a period of treatment with diet alone should be tried and if control remains inadequate additional treatment with insulin or a hypoglycæmic drug will be required.

Diet

Approximately 40 per cent. of diabetic patients can be controlled by diet alone. The diet should be designed with three objects in view :—

1. To stop the glycosuria.
2. To provide a pleasant, adequate and satisfying diet.
3. To bring the body weight as near as possible to the ‘ standard weight ’ for the patient’s age, sex and height.

Many doctors are intimidated by the number and variety of diet sheets published in some textbooks and feel that, since they are not trained dietitians, they cannot treat diabetes. A dietitian is certainly most helpful, but not indispensable.

The first step is to decide, from general principles, how much carbohydrate, protein and fat the diet should provide. The ‘ reference diet ’ (Diet 19) is suitable for the initial treatment of a case of moderate severity. This must be adapted to suit the patient’s accustomed food habits by making use of the system of exchanges as explained on page 609.

The carbohydrate intake must be restricted, to control the glycosuria, but should not be so low that the body is forced to metabolise fat excessively and thus develop ketosis. Sugar and sweets must be prohibited. Most diabetics in sedentary occupations do well on 145 to 220 g. carbohydrate/day. As little as 100 g. may be temporarily indicated in obese patients.

The protein intake should be ample, particularly since some may be used up in gluconeogenesis, before the biochemical lesion is properly controlled. The recommended allowance is that for a normal adult, *i.e.* the amount that will provide not less than 11 per cent. of the total calories (Chapter 5), or 60 to 120 g. of protein (Table 42, 1).

The fat intake should be adjusted to bring the total calories to the level desired for the control of body weight. The range will vary from 50 to 120 g.

The control of body weight.—The caloric intake should be determined by whether the patient is overweight, underweight, or of normal proportions ; in the latter case consideration must be given to his occupation and the expenditure of energy that it involves.

In obese diabetics the essential principle is to impose a restriction in calories, especially those derived from carbohydrates and fats, in order to bring the weight down to standard levels. This may be all that is needed to stop the glycosuria. Obese diabetics usually do not require insulin ; indeed, if possible it should not be given to them, as by increasing their appetite it adds to their weight and so intensifies their trouble. Insulin can be withheld from most obese diabetics without fear of dangerous ketosis.

On return to normal weight, the hyperglycæmia is reduced and the glucose tolerance may even be restored completely to normal.

In underweight or emaciated diabetics it is generally impossible to achieve all of the objectives listed above and abolish ketosis without the help of insulin. In practice, therefore, the principles are :—

1. To give enough calories to restore the body weight.
2. To give enough insulin to control the hyperglycæmia, abolish ketosis, reduce or abolish the glycosuria and enable carbohydrate to be retained.

Examples.—(1) An obese middle-aged housewife complaining of thirst, polyuria and pruritus vulvæ, with sugar but no acetone in her urine, will usually do well on a reducing diet such as Diet No. 1. No insulin is required. When the glycosuria and symptoms are relieved and a satisfactory reduction in the body weight has been achieved, the diet should be gradually increased.

(2) A man in the prime of life who is first seen a few weeks after an acute onset of severe diabetes may have already lost many pounds in weight. His mouth is parched and he is sleepless from constantly rising in the night to pass urine. His urine turns Benedict's reagent red. He exhales acetone. In such a case there is an urgent need for insulin. An initial diet based on Diet No. 19, providing approximately 2400 Cal. made up of 220 g. carbohydrate, 100 g. protein and 125 g. fat, with as much insulin as is necessary to enable the carbohydrate to be retained, will be found satisfactory. Later the diet (and perhaps the insulin dosage) should be gradually adjusted until the body recovers its normal weight. It is unwise that this should ever be exceeded ; *most diabetics receiving insulin keep*

in the best health if their weight is slightly below standard and their caloric intake definitely below average for people of the same sex, age and occupation.

(3) There remains the mild diabetic, neither overweight nor underweight, with few or no symptoms, often discovered by a chance examination of the urine and a subsequent glucose tolerance test. In such a case a simple restriction of foods rich in carbohydrates may be all that is necessary to avoid glycosuria and associated symptoms, and to keep the patient in health.

Management of the diet

As indicated in Chapter 2, it is impossible to predict from the height, weight, age and sex of a patient how many calories he or she is going to need without a precise estimate of daily energy expenditure. Such an estimate is usually lacking in clinical practice. Even a careful history of the nature of a man's work or a housewife's duties may convey a very imperfect idea of their daily caloric expenditure. A man in a modern ' heavy industry ' may do little more than sit and periodically press a button. The management of the diet in every case of diabetes, therefore, resolves itself into a matter of simple, empirical experiment. The initial diet prescribed is based on experience of the needs of patients of the same kind. Thereafter several adjustments may be needed—either up or down—until the caloric intake necessary to attain and sustain a satisfactory body weight is achieved. Further adjustments are often necessary to ensure that the diet is devised to suit the patient's individual habits. Thus a man who works periodically on night shifts may get into difficulty with no other guide than a printed diet sheet designed for three regular day-time meals. The empirical method allows for all the unpredictable factors that determine a patient's individual dietary requirements. A rough approximation of the calories, carbohydrate, protein and fat which will be required by diabetics, varying according to their build, age, sex and physical activities is given in Table 42, 1. These should serve as a guide for the prescription of a suitable diet for any individual patient. Medical supervision of each patient should be continued indefinitely, since any subsequent change of job or of domestic circumstances, or an intercurrent illness, may alter requirements in an unpredictable way and hence result in a change in nutritional needs.

Weighing the food.—The adjustment of the diet according to the needs of the individual patient demands that the diet prescribed should be accurately followed. This can only be achieved by weighing the food. As a general rule, therefore, diabetic patients should be provided with scales and instructed in how to use them. After some practice many intelligent diabetics learn to judge by eye with surprising accuracy a 1 oz. slice of bread, etc. With experience, therefore, it is often possible to regulate the diet with sufficient precision without the need for continued weighing of the food before each meal. Nevertheless it is worth noting that one distinguished Nobel prizewinner—Dr George R. Minot, Professor

TABLE 42, 1

(From Dunlop, Davidson and Alstead, 1961)

Type of patient	Calories†	Carbohydrates	Protein	Fat	Milk	Exchange of Carbohydrates	Exchange of Protein	Exchange of Fat
		g.	g.	g.	pints			
1. Child aged from 3 to 4 years *	1350	130	65	65	1	6½	3	1½
2. Child aged from 7 to 8 years *	1750	165	90	80	1	9	5	2
3. Child aged from 11 to 12 years *	2050	195	95	95	1	11	5	3
4. Child aged from 14 to 17 years *	2350	225	115	110	1	13	7	3
5. Young female shop assistant *	2200	225	110	95	1	13	6	2½
6. Woman in latter half of pregnancy *	2350	225	115	110	1	13	7	3
7. Hard working labourer *	2550	240	120	120	1	14	7	4
8. Middle-aged housewife treated with a sulphonylurea	1600	165	80	65	½	10	5	1½
9. Middle-aged sedentary man treated with a sulphonylurea	1900	180	90	90	½	11	6	3
0. Elderly, inactive woman treated by diet alone	1400	150	70	60	½	9	4	1½
1. Obese woman treated by diet alone	1110	105	60	50	½	6	4	1

The above are calculated on the basis that 1 carbohydrate exchange contains 1 g. of fat.

of Medicine at Harvard University—in the course of a long and useful diabetic life, continued to weigh his own food (Rackemann, 1956). Moreover, for many diabetic patients regular weighing of food is a useful discipline; it serves as a daily reminder that their continued health and well-being is dependent on accurate regulation of their food intake.

The diet.—Diet No. 19 gives the outline for a 'reference diet,' from which many different menus may be derived.

EXCHANGES.—The patient should be furnished with a list of exchanges in writing. With practice and intelligent use such a list provides a means of making the diet more varied and pleasant; it also enables the patient to adjust the diet to financial circumstances by choosing the foods that can best be afforded. Appended to Diet No. 19 is a list of exchanges suitable for use by a patient accustomed to a Western type of diet. Examples of exchange are shown at the top of the next page.

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* Indicates patients receiving treatment with insulin.

† The caloric intakes in this table are lower than the standards set out in Chapter 2, especially those for children. This is deliberate, because diabetics do better if slightly underweight. If these amounts prove inadequate to allow normal growth or to maintain weight, they must be increased.

Exchange			Carbohydrate	Protein	Fat	Cal.
Carbohydrate	Bread	1 oz. (30 g.)	15 g.	3 g.	1 g.	80
Protein	Lean meat	1 oz. (30 g.)	0	8 g.	5 g.	80
Fat	Butter	½ oz. (15 g.)	0	0	12 g.	110

This system of adding or subtracting appropriate exchanges inevitably introduces certain errors, since the nutrient values of the foods in each list are not precisely identical. Some of the foods listed as useful sources of carbohydrate also contain important amounts of protein (*e.g.* bread), while the meats listed as sources of protein are often also important sources of fat. Thus there is no consistency in the caloric value of the different exchanges. Obese diabetics whose caloric intake must be restricted should be warned of the particular foods they should avoid (p. 822). For other diabetic patients these inconsistencies can be ignored with safety, especially in view of the wide variations in composition between different samples of the same foodstuff. For the majority of diabetics treated as out-patients, though the caloric intake should certainly be estimated, it cannot be calculated with precise accuracy.

Diet No. 20 illustrates how the ' reference diet ' can be adapted, with the aid of the list of exchanges, to provide a menu suitable for a diabetic patient in Great Britain.

Diet No. 21 is entirely different in composition from Diet No. 20 and yet almost identical in nutritive value. With a list of exchanges comparable to those on page 847, based on local food analyses, it could be modified in a similar way to suit the individual tastes of the patient and the local prices of comparable exchanges.

Calculating the composition of the diet.—There are three levels of accuracy that may be desirable in the management of diabetes.

1. For out-patients and in general practice it is usually sufficient if the patient weighs the food to the nearest ½ oz. (15 g.), making full use of the lists of exchanges. Precise calculations of the nutrient value of each item of food is neither necessary nor desirable. The general practitioner, in fact, does not need to use food tables.

2. In hospital practice, on the other hand, it is sometimes necessary to measure the diet with greater precision. The help of a dietitian is then invaluable, to calculate the composition of the diet provided in terms of the proximate principles in each item of food as served. For this purpose she needs to be provided with an up-to-date copy of one of the food tables listed in Chapter 16.

3. For accurate metabolic balance studies, food tables are insufficient. They are particularly inaccurate in measuring the fat content of the diet. The assistance of a biochemist is therefore necessary to carry out a direct analysis of the proximate principles in exact duplicates of the meals served.

With these considerations in mind we have decided that no composite food tables should be included in this book. Sufficient general information on the nutrient content of foods has already been provided by the numerous tables in Part II. Every dietitian should have her own set of composite tables, suited to the country in which she works and the foods with which her patients are familiar. Such tables should be based on food analyses carried out locally, or at least in the same general environment, since the composition of an individual foodstuff may vary remarkably from one country to another. Thus the carbohydrate content of a sweet potato may be very different in North America from that found in India.

Adjusting the diet to the dosage of insulin.—In patients requiring treatment with insulin it is often necessary to adjust the amount of carbohydrate in each meal, so that the largest part of the daily carbohydrate allowance is taken when the insulin is exerting its maximum effect on the blood glucose. This will depend on the type of insulin used, as described in the next section. By testing for glucose specimens of urine obtained at selected times (p. 616), it is usually possible to tell whether the insulin dosage has been sufficient to ‘ cover ’ the carbohydrate ingested at the previous meal. If glycosuria is found at some particular time in the day, it is often satisfactorily corrected by redistributing the carbohydrate allowance between the three main meals, without increasing the dosage of insulin.

Sweetening agents.—One of the hardships which many diabetics feel when their carbohydrate intake is restricted is the lack of sweet foods. Indeed it is often a ‘ sweet tooth ’ that has led to obesity and thus brought out the diabetic symptoms. Whenever possible, it is desirable to break the patient’s craving for sweet foods. Sugar in tea, the sugar bowl on the dinner table, sweetened fruit drinks, sweetened synthetic drinks, sweet heavy wines (*e.g.* sherry) should all be forbidden. However, it sometimes happens that the future co-operation of the patient is jeopardised by these prohibitions, so great is the craving for sweet foods. It is then sometimes justifiable to indulge the patient by permitting the use of saccharin in place of sugar ; but so long as this is allowed, the temptation to partake of surreptitious sweets remains.

In recent years a large industry has grown up, marketing ‘ diabetic ’ chocolate, fruit drinks and preserves in great variety. The sweetening agent used in their manufacture is sorbitol. This derivative of glucose is slowly absorbed from the gut and so produces no immediate or important increase in the level of glucose in the blood, as already explained in Chapter 4. On the other hand sorbitol is eventually absorbed, and so contributes to the total caloric intake. In obese diabetics, faced with the necessity of losing weight, ‘ diabetic ’ foods provide no escape from the unpleasant necessity of avoiding all sweet foods. For such patients, food sweetened with sorbitol is an indulgence that should not be allowed. A further objection to ‘ diabetic ’ foods is their cost.

General.—The proper management of the diet calls for the utmost tact and sympathy on the part of the dietitian interviewing the patient. Some apprehensive patients are so meticulous in their desire to follow instructions that they tend to spend overmuch time in precisely weighing every item of food, and complain that the scales with which they have been supplied are not accurate enough to record to the nearest 1 g. Others of the ‘ couldn’t care less ’ kind need to be repeatedly told that their salvation lies in having the scales constantly before them at each meal.

INSULIN

Approximately 40 per cent. of all diabetics will require insulin if the disease is to be properly controlled.

Ever since insulin first became available for therapeutic use it has been argued that it should be possible to keep the blood glucose within normal limits throughout the 24 hours, day after day, so that the patient is biochemically normal and no possibility of complications arises. Unfortunately no method of giving insulin has yet been found that will infallibly prevent hyperglycæmia occurring at some time throughout the 24 hours without causing interludes of hypoglycæmia. However, every effort should be made by appropriate use of one or more of the preparations of insulin available (adjusted to the needs of the individual patient) to keep the blood glucose within reasonable limits throughout the day and night.

Well-controlled diabetics are believed to be less liable to the complications discussed on page 621 than those whose diabetes is unstable or uncontrolled. Part of this control involves the maintenance of a satisfactory blood glucose level that fluctuates within narrow limits. While there is no direct evidence that hyperglycæmia *per se* is the immediate cause of any of these complications, it must be remembered that vascular degeneration in diabetes may be due to a defect in the metabolism of mucopolysaccharides which may result, in turn, from defective utilisation of glucose.

The dosage of insulin is best regulated initially by periodic estimations of blood glucose which should ordinarily not exceed 175 mg./100 ml. of blood taken just before meals (p. 603). Such a test is particularly valuable in detecting patients with a low renal threshold for glucose who may develop hypoglycæmia from too much insulin while continuing to have glycosuria. It will also detect the patient with a high threshold, who, despite satisfactory urine tests, nevertheless may have considerable hyperglycæmia requiring an increase in the dosage of insulin.

Once the extent of the hyperglycæmia to which the patient is liable has been determined, the day-to-day insulin dosage can ordinarily be regulated by testing selected specimens of urine for glucose. For further details of assessment of diabetic control by such tests, see page 616.

Insulin is a protein derived from the pancreas of animals. It is destroyed in the digestive tract, and no effective method of giving it other than by parenteral injection has yet been found. Although the precise chemical structure of insulin has been elucidated, there is no immediate hope that it can be produced by laboratory synthesis. Thirty years of research have so far failed to find a satisfactory synthetic substitute for it. The only patients who cannot learn to give their own injections of insulin are those who are very young, stupid, blind or disabled.

Ordinary or soluble insulin, when injected subcutaneously in a dose of about 20 units, exerts its maximum effect on the blood glucose in 2 to 6 hours. The effect wears off in 5 to 8 hours. A patient on soluble insulin, therefore, usually needs at least two injections in the day. In a typical case of moderate severity the dose found necessary will be between 10 and 20 units, twice daily.

However, the advantages of the depot insulins (described below) are so great that they are now preferred in the treatment of diabetes, except in the following circumstances where soluble insulin still fulfils a vital need : (*a*) in emergencies, such as ketosis, acute infection, gastro-intestinal upset or surgical operation ; (*b*) in individual patients whose food intake or glucose tolerance fluctuates widely (and sometimes unaccountably) from day to day, as may happen particularly in diabetic children and adolescents.

Soluble insulin controls the blood glucose quickly, reproducing the effect of the rise in natural insulin secretion in a normal person, following a meal containing carbohydrates. The effect of soluble insulin wears off rapidly, so that subsequent doses can be altered throughout the day according to the amount of glucose found in the urine. It therefore provides an elastic method of treatment that can be adapted to the circumstances of the moment.

'Depot' or slow-release insulins have the advantage that with their aid the majority of patients requiring insulin, with mild to moderately severe diabetes, can be controlled by a single injection first thing each morning. They resemble in their action the small, continuous natural secretion of the pancreas ; but unlike the natural secretion, they fail to deal effectively with the rise in blood glucose which results from a meal containing carbohydrates. The most useful of the depot insulins is **protamine zinc insulin.**

Protamine zinc insulin (PZI).—The addition of protamine and zinc to ordinary insulin has the effect of delaying its release from the site of injection, so that PZI exerts its maximum effect on the blood glucose in 8 to 14 hours ; the effect wears off in 16 to 24 hours ; the larger the dose the longer the effect. Despite its prolonged action PZI is rarely capable of keeping the blood glucose within satisfactory limits throughout the 24 hours. Excessive glycosuria is most likely to occur in the forenoon before the morning injection has taken full effect, consequently a supporting dose of soluble insulin is usually needed in the morning and sometimes again in the evening. This is particularly the case when, because of the severity of the diabetes, large doses of insulin are needed. If the morning dose of PZI is further increased this may result in severe hypoglycæmia later in the day or at night. In general, the dose of PZI should rarely exceed 40 units at a single injection : hence the need for supporting doses of soluble insulin.

Insulin zinc suspensions were first introduced in 1953. The slow release of these insulins from the tissues is largely due to the size of the insulin particles which are suspended in acetate buffer. Three preparations are available :—

1. *IZS Amorphous* (*semilente*) has a duration of action which is only slightly shorter than that of PZI.
2. *IZS Crystalline* (*ultralente*) has an action that is slower in onset than IZS Amorphous, reaching a maximum in 8 to 14 hours and not wearing off for 16 to 20 hours.
3. *IZS* (*lente*) consists of a mixture of three parts of the amorphous to seven parts of the crystalline material. It has been found in practice that this usually achieves the most uniform reduction of the blood glucose over the 24 hours between each injection. This mixture is regularly dispensed when IZS is prescribed unless the prescription specifically orders IZS Amorphous or IZS Crystalline, either alone or in different proportions.

Globin insulin is another depot insulin, intermediate in duration of action between soluble and PZI insulin. It has been largely replaced in clinical practice by IZS (lente).

The advantages and disadvantages of depot insulins

IZS (lente) insulin is probably the preparation of choice for the control of mild or moderate cases, requiring less than 40 units daily ; but with larger doses, prolonged and profound hypoglycæmia may result without warning. Severe diabetics are therefore safer on PZI with supporting doses of soluble insulin.

Insulin zinc suspensions contain no protamine or other added protein products. For this reason they cause fewer local allergic reactions than PZI at the site of injection.

The chief disadvantage of the insulin zinc suspensions is that they cannot be injected (like PZI) in the same site with soluble insulin, since the slightly acid *p*H of the latter alters the particle size of the suspensions, and hence their rate of absorption.

The disadvantage of all depot insulins is that the dose cannot be adjusted satisfactorily to meet any sudden and unexpected change in requirements such as may be occasioned by an infection, surgical operation or gastrointestinal upset. In all such emergencies, soluble insulin remains the preparation of choice.

Measurement and injection of insulin and the care of the syringe

The great majority of diabetics are capable of being instructed by the doctor or dietitian in the technique of measuring the dose of insulin prescribed and the method of injecting it. For these purposes only a

TABLE 42, 2

Type of insulin	Times of effective action in hours		
	Start	Maximum	Duration
1. Quick and short acting—			
Soluble—dose of about 20 units	½	2–6	5–8
Soluble—dose of 40 or more units	½	4–9	8–12
2. Intermediate acting—			
Globin	2–3	6–12	8–14
IZS Amorphous	2–3	4–10	8–12
3. Slow and long acting—			
PZI—dose of about 20 units	4–6	8–14	16–24
PZI—dose of 40 or more units	4–6	12–20	24–32
IZS Crystalline	4–6	8–14	16–20
4. Mixture of IZS Amorphous and IZS Crystalline—			
IZS (lente)	2–4	6–14	16–20

standard type of insulin syringe should be used, *e.g.* B.S. 1619. These syringes are graduated in 20 marks to the ml. so that one mark on the syringe equals 2 units of 40 strength insulin or 4 units of 80 strength insulin. The syringe and needle should be kept in surgical spirit in a tray or in a water-tight metal or plastic case by those who have to carry it with them. Insulin is given by deep subcutaneous injection and the site of injection (outer aspect of thigh, upper arm, lower buttock or lower abdominal wall) should be varied from day to day. For further details of the technique of filling the syringe with a single insulin or mixture of insulins, cleaning the skin, inserting the needle into the tissue, making the injection and preventing or treating any undesirable local complications which may occur, the reader should consult a textbook of medicine or therapeutics (Dunlop, Davidson and Alstead, 1961).

DIET AND ORAL HYPOGLYCÆMIC AGENTS

The sulphonylureas.—The search for a satisfactory oral substitute for insulin has been actively pursued in recent years. Certain sulphonylureas have been found to lower the blood glucose. Of these the most generally useful are tolbutamide and chlorpropamide. Tolbutamide is quickly excreted and is therefore generally given in two daily doses of 0·5 to 1·5 g. each. Chlorpropamide has a more prolonged action ; a single morning dose of 0·1 to 0·25 g. is sufficient to control hyperglycæmia in selected cases. It is also considerably cheaper and hence is the hypoglycæmic drug of choice. The incidence of toxic reactions is low when the maximum dose, which is 0·4 g. daily, is not exceeded.

The diguanides.—The mechanism of action of the diguanides is not known, but they may act by facilitating the uptake of glucose by the peripheral tissues. Their tendency to cause nausea, vomiting and diarrhœa when given in doses sufficient to lower the blood glucose to an effective level is a serious disadvantage. They may be tried in cases which were selected for treatment with a sulphonylurea and which failed to respond or which developed in time a secondary resistance. For this purpose phenformin (Dibotin) 25 mg. or metformin (Glucophage) 0·5 g. twice or thrice daily after meals can be tried. The dosage is increased every 2 to 3 weeks until satisfactory control is obtained or the degree of toxic effects necessitates the abandonment of treatment.

The use of oral hypoglycæmic drugs should be restricted to the treatment of patients suffering from mild diabetes who are over 35 years of age, who fail to respond adequately to dietetic measures alone and who would otherwise need a small daily injection of insulin. For the aged, infirm and blind, these new drugs are certainly a great relief, both to the patient and to the nurse who previously had to visit them daily to give their injections. Approximately 20 per cent. of all diabetics can be controlled satisfactorily by diet and an oral hypoglycæmic agent.

Assessment of Diabetic Control

The efficiency of the treatment of a case of diabetes is assessed on the basis of the clinical state of the patient and by the result of tests for glucose in selected samples of blood and urine. If these tests are not carried out properly, the results obtained may be not only incorrect but gravely misleading. Measurement of the blood glucose concentration is of value in assessing the severity of the diabetic state and is essential for determining whether the renal threshold for glucose is low, normal or high. These matters have been referred to on page 603. In practice, both in hospital and in the patient's home, and irrespective of whether the patient is being treated by diet alone, by diet and insulin or by diet and oral hypoglycæmic drugs, the disease can usually be controlled by tests for glucose in the urine. Accordingly it is essential that every diabetic patient is instructed in the use of the ' Clinitest ' apparatus, which not only indicates whether glucose is or is not present, but also enables an approximate quantitative assessment to be made. The patient must also be taught how to keep in a notebook a record of the results of the tests he has carried out. Lastly it must be explained to him that the object of these tests is to get an idea of the level of glucose in the blood at special times and this can only be accomplished if the patient invariably empties his bladder half to one hour before carrying out the test and discarding this specimen. Half an hour later he passes urine on which the test is performed. By selecting suitable times for the tests and charting the results it is easy for the doctor, and later the patient, to decide whether the dose of insulin or hypoglycæmic drug should be increased or reduced, or whether the carbohydrate content of the diet should be altered or redistributed.

In the initial stage of control of a patient on insulin, tests for glucose in the urine will have to be carried out three or four times daily, but after control has been established the frequency of such tests can be greatly reduced. The four most important samples of urine for testing are : (1) the pre-breakfast sample which reflects the fasting blood sugar ; (2) and (3) the pre-lunch and pre-supper samples which reflect the blood sugar levels before these meals ; (4) the ‘ pre-bed ’ sample which consists of urine passed not earlier than 3 hours after supper. This reflects the blood glucose level immediately before the patient retires to sleep.

For the control of patients with mild diabetes on treatment with diet alone or diet and sulphonylurea, the most important specimens of urine to be tested are those passed 2 hours after the two main meals.

The general practitioner can usually decide whether his diabetic patient is under proper control by considering whether there are (*a*) symptoms ; (*b*) changes in weight ; (*c*) glucose in the specimens of urine collected at the times stated above.

If there is any reason to suspect that the hyperglycæmia is not under control the patient should be referred to a hospital for a blood glucose determination.

All but a very few patients can be taught to test their own urine for glucose and keep their diabetes controlled thereby, though too frequent ‘ home tests ’ should be discouraged in over-anxious patients. Tablets are also available which enable the patient to test his own urine for ketone bodies ; these are sometimes useful (*e.g.* during an intercurrent illness) as an aid to the patient in helping him to decide whether he ought to seek immediate medical advice.

The early detection of loss of control of the diabetic state, as indicated by excessive glycosuria or slight ketosis, is essential if patients are to be kept at their work and out of hospital. Patients should be encouraged to come to their doctor or to the clinic at once, on their own initiative and without prior appointment, as soon as they are aware of anything wrong.

HYPOGLYCÆMIA (INSULIN ‘ REACTIONS ’)

If soluble insulin is administered to a normal person the blood glucose falls, producing symptoms that begin to appear when the blood glucose level is about 60 mg./100 ml. and are fully developed at about 40 mg./100 ml. In diabetics accustomed to hyperglycæmia the same symptoms may develop at a much higher level of blood glucose, *e.g.* 120 mg./100 ml.

The symptoms of hypoglycæmia due to too much soluble insulin in order of frequency are : a feeling of being weak and empty (hunger) ; sweating ; seeing double ; tachycardia and palpitation ; tremor ; faintness, dizziness, occasional headache ; mental confusion, hysterical behaviour, leading occasionally to arrest by the police on a charge of being drunk and disorderly. Alternatively, in children especially, there may be lassitude and somnolence ; muscular twitchings ; deepening coma, and convulsions.

The sweating, tachycardia and tremor are due to stimulation of the sympathetic nerves which in turn stimulate the secretion of adrenaline from the adrenal glands. Adrenaline, by mobilising liver glycogen, combats the hypoglycæmia. This homeostatic reaction on the part of the body probably explains why patients rarely die of hypoglycæmic coma from too much soluble insulin. The danger of serious coma is mainly from the use of large doses of depot insulins. Hypoglycæmic coma is usually a minor emergency compared with diabetic coma. Nevertheless it should be remembered that repeated incidents of profound hypoglycæmia may lead to permanent mental changes, because the brain is entirely dependent on a steady supply of glucose from the blood for the energy necessary for its continued activity. Though seldom fatal, hypoglycæmia is an accident which should be prevented from recurring by prompt reduction of the dosage of insulin.

Hypoglycæmia due to overdosage with soluble insulin comes on relatively rapidly, *i.e.* from 2 to 6 hours after the injection. Hypoglycæmic reactions from too much IZS (lente) given before breakfast occur in the late afternoon and those from PZI at night or early next morning ; while beginning gradually and undramatically they may become persistent and profound unless vigorously treated. The symptoms are different.

Symptoms of hypoglycæmia due to depot insulins may be : headache ; malaise ; night sweats ; nausea leading sometimes to troublesome vomiting ; mental confusion ; drowsiness, especially in the morning ; and coma.

Treatment of hypoglycæmic reactions.—Every patient taking insulin should be given deliberately an insulin reaction so that he recognises the symptoms and thus knows how to forestall it. The most common causes are a delayed or missed meal and unaccustomed exercise, and on the first recognisable symptom it is usually sufficient simply to expedite the next meal. In case this is not immediately possible, several lumps of sugar should always be carried, to be taken in emergency. Following an attack of hypoglycæmia, the next day's dose of insulin should be reduced by 4 units or so, unless there has been some unaccustomed physical exertion, since this can precipitate hypoglycæmia. Knowledge of these principles has greatly reduced the number of diabetics now brought to hospital in hypoglycæmic confusion. Glucose by mouth is all that is usually necessary to bring such patients to their senses. Only if the patient is too stuporous to swallow is it necessary to give glucose by stomach tube or intravenously. For the latter purpose 30 to 50 ml. of a 50 per cent. solution of glucose is usually adequate. A subcutaneous injection of 0·5 ml. of 1 in 1000 solution of adrenaline usually awakens an unconscious patient within a few minutes and enables him to swallow a solution of glucose. Recently preparations of glucagon (p. 60) have become available for this purpose. As glucagon is very effective and so safe that a relative or other lay person can be entrusted with its administration, it should replace adrenaline in the treatment of hypoglycæmic coma. A dose of 0·5 to 1 mg. of glucagon can be given subcutaneously and will usually awaken the patient in 5 to 20 minutes. If there is delay in response an additional 1 or 2 mg. may be given.

Confusion between the coma due to hypoglycæmia and that associated with ketosis should seldom arise ; the distinction is clear.

Differential Diagnosis

	HYPOGLYCÆMIC COMA	DIABETIC COMA
History :	No food. Too much insulin. Unaccustomed exercise.	No insulin. An infection. Digestive disturbance.
Onset :	In good health immediately before. Related to time of last injection of insulin.	Ill-health for several days before.
Symptoms :	Of hypoglycæmia (p. 617).	Of glycosuria and dehydration (p. 620).
Signs :	Moist skin and tongue. Full pulse. Normal or raised blood pressure. Shallow or normal breathing.	Dry skin and tongue. Weak pulse. Low blood pressure. Laboured breathing (‘ air hunger ’).
Urine :	No ketonuria. No glycosuria, provided that the bladder has been recently emptied.	Ketonuria. Glycosuria.
Blood :	Hypoglycæmia. Normal CO_2 combining power.	Hyperglycæmia. Reduced CO_2 combining power.
Frequency :	Common.	Rare.

It should be noted that diabetic coma may occasionally pass, undetected, into hypoglycæmic coma through too enthusiastic treatment ; likewise, vomiting induced by hypoglycæmia from a depot insulin may continue until diabetic coma results.

KETOSIS AND COMA

The term ‘ diabetic ketosis ’ is better than the traditional ‘ diabetic coma ’ as a description of this grave complication, because coma suggests that unconsciousness is an essential feature, whereas it is imperative in practice that treatment should be started at the earliest ‘ pre-coma ’ stage. The *history* of events immediately ante-dating the onset of severe ketosis may reveal neglect of prescribed insulin, neglect of prescribed diet, or vomiting, or a carbuncle or other infection. Neglect of insulin or diet may be due either to carelessness or to a gastrointestinal upset or other illness.

Clinical features.—Many of the clinical features of diabetic ketosis are directly due to the dehydration and acidæmia which always accompany severe ketosis. They have been summarised in the scheme on differential diagnosis on page 619. Sometimes, inexplicably, there is abdominal pain or, more frequently, vomiting. Hence diabetic ketosis is important in the differential diagnosis of the acute abdomen.

If the patient is unconscious the emergency is one of the most urgent in medical practice. Even before consciousness is lost, immediate treatment is essential ; *a patient with dangerous ketosis may walk into hospital.*

Laboratory tests show (1) ketone bodies and sugar in the urine ; and (2) sometimes leucocytosis which, combined with abdominal symptoms and signs, may wrongly suggest an ‘ acute abdomen.’

In the days before insulin treatment, more than 50 per cent. of diabetics ultimately died of ketosis ; now ketosis accounts for less than 2 per cent. of diabetic deaths.

Treatment.—This dangerous complication requires prompt treatment *in hospital.* The aim should be :—

1. To stimulate carbohydrate utilisation by means of insulin.
2. To correct acidosis, dehydration, electrolyte depletion and consequent circulatory collapse by means of appropriate intravenous fluids.
3. To treat infection if present, by means of antibiotics.

Ketosis and dehydration render the comatose patient very resistant to insulin. Only *soluble* insulin should be used, 50 units being given immediately, and preferably intravenously while waiting for the ambulance. A patient may need 500 units in the first 24 hours. Much of this (*e.g.* 150 to 300 units) should be given early, in the first 3 hours. The mortality from coma is greatly reduced by giving insulin early and in adequate amounts. One litre of normal saline should be given intravenously as soon as possible, followed by more fluids, preferably including saline-lactate and sometimes 5 per cent. glucose as shown in Fig. 42, 2. In the presence of severe shock and low blood pressure, saline alone may be insufficient to revive the patient. In such a case an initial transfusion of blood or plasma may be life-saving. If the stomach is distended or if there is repeated retching, gastric aspiration, followed if necessary by gentle lavage, should be undertaken. Even when the patient is able to swallow, fluids given by mouth may be poorly absorbed ; intravenous fluids are therefore necessary. Treatment must be controlled by repeated tests for glucose and ketone bodies in the urine and by the estimation of the blood glucose and the carbon dioxide combining power of the blood.

When glucose and also amino acids begin to pass into the tissues under the influence of insulin, they carry with them potassium from the blood.

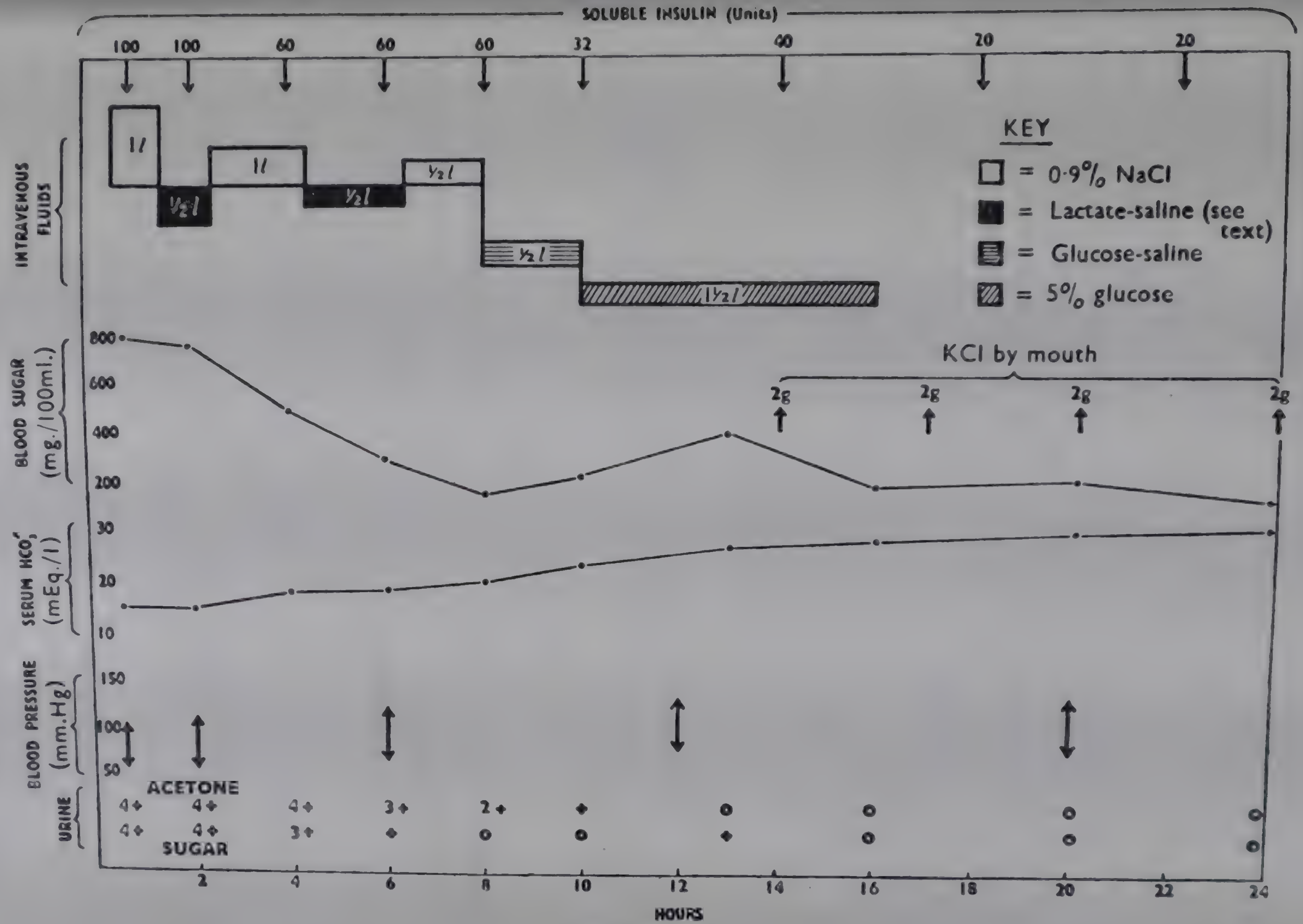


FIG. 42, 2

Chemical pathology and response to treatment of a moderately severe case of diabetic ketosis during the first 24 hours in hospital.

Any considerable fall in serum potassium results in severe and sometimes fatal consequences (p. 148). Potassium salts should therefore be given during recovery from diabetic coma. They should not be given while the patient is still severely dehydrated or before the injected insulin has begun to take effect, since under such conditions the level of potassium in the blood may be greater than normal. Potassium salts should be given by mouth for 2 or 3 days. Potassium citrate or chloride, 2 g. every 3 or 4 hours should be adequate. Once ketosis has been overcome, and the water and salt deficit made good (usually in about 24 hours), feeding by mouth can be started with frequent small fluid feeds each containing about 25 g. of carbohydrate. Five examples of such feeds are :—

(1) 3½ oz. fruit juice.
½ oz. sugar

(2) 3½ oz. milk.
4 tablespoons of porridge.

(3) 7 oz. milk.
¾ oz. Ovaltine, Horlicks or similar preparation.

(4) ⅓ pint milk.
⅓ oz. cereal.
¼ oz. sugar.

(5) 7 oz. milk.
⅔ oz. Benger's food.

Enough insulin should be given to prevent any further ketonuria or glycosuria. Only soluble insulin should be used for several days, until the patient is stabilised.

COMPLICATIONS

General.—When a patient is first recognised as having diabetes, a most careful appraisal of his general condition is necessary ; particular search should be made for early evidence of any of the complications listed below ; *e.g.* examination of the cardiovascular system for evidence of disease and hypertension, the peripheral vessels for obliterative arterial disease, the nervous system for peripheral neuropathy, the eyes for cataract or retinopathy, the urine for nephropathy, and radiological examination of the chest to exclude pulmonary tuberculosis.

Once treatment is begun *diabetics should be seen at regular intervals for the remainder of their lives.* The object of these visits is to check the degree of control of the diabetes and to watch for the development of complications.

The frequency of these essential, regular visits must be determined by the severity of the case and the trust that can be placed in the patient to carry out instructions.

Vascular changes.—Uncontrolled diabetes mellitus of long standing predisposes to degenerative changes in blood-vessels of all sizes.

IN THE CAPILLARIES.—Proliferation of the basement membrane develops, probably due to disordered metabolism of the mucopolysaccharides of which it is largely composed. This degenerative change in the capillary walls is responsible for serious disorders of vision and renal function.

IN THE ARTERIES.—Atherosclerosis occurs more commonly and extensively in diabetic than in normal subjects, rendering them more prone at an earlier age than other people to intermittent claudication, gangrene of the feet, myocardial infarction and nephrosclerosis. Seventy-five per cent. of diabetics ultimately die from the effects of one or other of these vascular disorders.

TREATMENT.—In the absence of sufficient knowledge of the cause of atherosclerosis (p. 557), it cannot be prevented in diabetics any more than in other patients. It seems logical, however, to assume that its special prevalence in diabetes may be due, in part at least, to the hyperglycæmia and lipæmia which are commonly present. These can be largely prevented by regular control of the diabetes. The treatment of cardiovascular disorders arising in diabetes as a result of atherosclerosis is the same as in other patients, with the added problem of controlling the diabetes.

DIABETIC GANGRENE.—Defective circulation in the legs may be due to the specific changes in the capillaries and arterioles described above or to atherosclerosis. The dangerous complication of gangrene may follow. It usually starts in one foot, following a trivial injury—the cutting of a corn or a burn from a hot-water bottle. Toxic absorption from necrosis of tissue and secondary infection may kill the patient unless the limb is amputated. Amputation of a toe, a foot, or even a whole leg is sometimes necessary to save life.

A great deal can be done to prevent this serious complication by telling diabetics with poor circulation to wear proper shoes, to use bed-socks rather than hot-water bottles, never to cut their own corns and to ‘ keep their feet as clean as their face.’ The services of a skilled chiropodist are invaluable.

Infections.—Any type of infection is of importance in diabetes, particularly if the disease is inadequately controlled. Especially important are :—

CARBUNCLE.—Staphylococcal infections often cause a large increase in insulin requirements. The development of a carbuncle may unmask latent diabetes ; it may even precipitate ketosis and coma. The diabetic state brought on by a carbuncle is not invariably permanent ; glucose tolerance may return to normal (at least temporarily) when the infection subsides.

Cleanliness is a special virtue in the prevention of skin infections in diabetes. Once infection has occurred a suitable antibiotic must be used.

PULMONARY TUBERCULOSIS.—If a diabetic under treatment shows unexplained loss of weight, increase in insulin requirements or other suggestive symptoms, clinical and radiological examination of the lungs should be undertaken. Pulmonary tuberculosis may be arrested in its early stages by prompt recognition and specific treatment.

URINARY TRACT INFECTIONS.—The presence of sugar in the urine provides a favourable medium for the growth of bacteria. Infections of the urinary tract frequently occur, and these may be difficult to eradicate. For this reason catheterisation should be avoided if possible. Once infection has occurred treatment consists in controlling the glycosuria and the administration of suitable antibiotics.

Ocular disorders

Blurring of vision.—This is a common complaint when diabetics first start insulin treatment. It is due to changes in the osmotic pressure in the lenses which occur when the level of blood glucose is rapidly lowered. When the disease is under control this feature usually disappears. Patients should therefore be reassured and dissuaded from wasting money on spectacles.

Diabetic retinopathy has a specific appearance which sometimes enables the physician to make the initial diagnosis of diabetes. On examination with an ophthalmoscope, microaneurysms on the capillaries and circular hæmorrhages and exudates may be seen. These are the consequences of the degenerative change in the capillaries mentioned above.

Very rarely a *specific* type of opacity of the lens (*cataract*) occurs in diabetic children whose disease has not been adequately controlled. Cataract also occurs in elderly diabetics, but is said to be no more common than in other elderly people.

Retinopathy unfortunately arises despite every effort both by patient and doctor to keep the diabetes regulated. More strict control might perhaps reduce its incidence and prevent its progress.

Diabetic nephropathy.—A specific type of renal lesion may occur as a result of the changes (mentioned above) in the glomerular capillaries. This is known as *intercapillary glomerular sclerosis*. The pathologist can make a retrospective diagnosis of diabetes on seeing nodular masses of dense hyaline material in the glomeruli. This histological finding is present in the kidneys in 65 per cent. of persons dying from diabetes. However, only 15 per cent. of these patients have clinical evidence of renal failure as shown by proteinuria, hypoproteinæmia, œdema, hypertension and nitrogen retention (Kimmelstiel-Wilson syndrome). The clinical picture is often complicated by pyelonephritis.

Diabetic neuropathy.—Peripheral neuropathy is a frequent and troublesome complication. Motor, sensory or autonomic nerves may be involved, usually, in a symmetrical manner. The most common types are :—

1. Acute peripheral neuritis which occurs especially in poorly controlled severe diabetics and which attacks one or many nerves. The clinical features are those of peripheral neuritis (p. 443). Pain, especially in the legs at night, is prominent. It is thought to be a metabolic neuritis and hence it usually improves rapidly when the diabetes is controlled.

2. Chronic peripheral neuropathy which is probably due to ischæmic damage to the sensory portions of peripheral nerves consequent upon

diabetic angiopathy, and is therefore more common in older diabetics with long-standing disease. The clinical features are those of a painless neuropathy affecting the legs and closely resembling those of tabes dorsalis (p. 443).

3. Involvement of the sympathetic autonomic system which may cause diarrhœa, overflow retention of urine, impotence or postural hypotension.

SPECIAL PROBLEMS IN THE MANAGEMENT OF DIABETES

There are three situations in which the control of diabetes may create special difficulties in the management of the diet and of insulin administration. These are : in childhood, especially at puberty ; during pregnancy and confinement ; and before and after surgical operations. Each of these will now be considered.

DIABETES IN CHILDREN

Fortunately diabetes does not commonly begin in childhood, but when it does it is usually relatively severe from the outset, and always requires treatment with insulin. The therapeutic problem of matching the dose of insulin to the food intake often raises various practical difficulties which can be considered under the following two heads :—

FOOD.—The nutritional needs of diabetic children are essentially no different from those of other children. Since they are (or should be) growing, their caloric requirement is large in proportion to their size, by comparison with adult standards (Table 15, 1, p. 254). This large caloric requirement may be enhanced by the fact that some diabetic children are unusually tall for their age. Difficulties may be experienced in finding the best means of providing the requisite calories. In children, likes and dislikes for particular foods are often fickle and unpredictable.

Dietetic wisdom and experience are needed to find the proper regime that suits each individual patient. It should be remembered that the child's bones are growing. A high intake of calcium—best supplied by milk and cheese—is desirable to promote their growth. It is important to make sure that the child does not become too fat ; hypoglycæmia, due to too much insulin, can lead to excessive appetite, and hence to obesity.

INSULIN.—A diabetic child's day-to-day requirements for insulin are often very variable. Few children lead the steady life of an adult business man or housewife ; their emotions and activities fluctuate unexpectedly—sometimes wildly active and sometimes sulking. This may have an important effect on their daily needs for insulin ; excessive activity may result in hypoglycæmia, whilst lethargy may lead to hyperglycæmia. The latter may also be caused by any one of the numerous infectious diseases to which all children are prone. A combination of PZI and soluble insulin before breakfast and if necessary a second dose of soluble insulin before supper is a suitable arrangement.

Management.—With proper attention and care, none of these difficulties is insurmountable. The diabetic child must learn to understand about his disease, and rely on his medical adviser for proper guidance. He should learn early (at about 7 to 8 years) to give his own injections, and know how to adjust the dosage to his activities. He should also know that he must warn his parents the moment he feels ill. Experience has shown that many people who have suffered from diabetes since early childhood have grown up to be strong and effective members of society. They have succeeded by discipline, self-imposed.

The diet.—A dietitian can do much to help a diabetic child and his parents with proper advice. It is important that he should feel no different from other children, except that he must not fail to inject himself regularly with the prescribed dose of insulin, and must follow his dietetic instructions. The essential composition of his diet need differ little from that of his friends, but diabetic children should be discouraged from tasting sugar or sweets. Once properly trained, he may go with them to a summer holiday camp if he so desires, provided that the camp organiser understands his disease. The British Diabetic Association runs special camps.

Diet No. 22 is suitable for a diabetic child of 4 to 6 years. It would be equally suitable for a normal child of the same age.

Pregnancy in Diabetes

One of the important consequences of the discovery and use of insulin is that diabetic women can now have children, whereas in the pre-insulin era they were almost always amenorrhœic and infertile. If a diabetic woman wishes to have a child there is no reason why she should avoid pregnancy, provided that she suffers from none of the more serious complications of diabetes listed on page 621 and provided she is under expert medical care. With proper supervision available, uncomplicated diabetes need not be regarded as an indication for birth-control, sterilisation or therapeutic abortion.

Nevertheless it must be emphasised that pregnancy in a diabetic woman carries certain definite risks ; in the later stages of pregnancy she may develop an excessive accumulation of the fluid surrounding the fœtus (hydramnios) ; in addition the fœtus is sometimes unusually large, and liable to die, either shortly before delivery or soon after birth. The chances that a diabetic mother may lose her baby either from a stillbirth or in the early neonatal period are greater than those of a non-diabetic mother. However, with proper care these risks can be so greatly reduced that all over the world to-day there are now very many happy diabetic mothers.

The proper treatment of a pregnant diabetic patient requires the close and co-ordinated supervision of a team, consisting of a physician, obstetrician, anæsthetist, nurse and dietitian. The sooner the pregnancy is diagnosed the better. Some non-pregnant diabetic women often miss one or more menstrual periods, especially if their disease is poorly controlled. For this reason a Hogben pregnancy test is often helpful. It is desirable that the expectant mother should spend a week as an ambulant in-patient in hospital, towards the end of the third month of pregnancy. This will enable the team to get to know her, and she them. Much depends on establishing mutual trust and co-operation from the outset. Every effort must be made at this time to see that her diabetes is under the best possible control ; further education of the patient may be needed in the proper management of her diet and insulin while at home. The diet, at first at least, need differ in no important respect from the one to which she has been accustomed. If more calories are needed, Diet No. 20 will be found satisfactory, with the addition of an extra pint of milk. The general principles laid down in Chapter 57 for the management of the diet in normal pregnancy apply equally well to diabetics. Practical problems may be created for the physician and dietitian by bouts of vomiting that commonly occur in the early stages of any pregnancy, and by the peculiar food fads which many pregnant women develop (Chapter 57).

After the diagnosis of pregnancy has been made the patient should be seen at first, at fortnightly, and later at weekly intervals. Continued full control of the diabetes may be complicated by other factors. First, the renal threshold for glucose often falls as pregnancy advances. This is a normal phenomenon ; but in the diabetic it means that the tests for glycosuria which she carries out at home may cease to be a reliable index of diabetic control. Further, in the later stages of pregnancy some lactosuria may occasionally occur and leads to confusion. Then, too, the requirements for insulin often increase as pregnancy advances. Frequent estimations of blood glucose are needed to ensure that an increase in insulin dosage, based on misleading urine tests, is not producing hypoglycæmia ; or alternatively, that hyperglycæmia is not insidiously building up through failure to give enough insulin to meet an increase in insulin requirements.

Pregnancy in a diabetic woman should seldom if ever be allowed to proceed to term. The chances of survival for the infant are greatly enhanced if it is delivered at about the thirty-sixth week by Cæsarean section or by induction of labour. Following delivery the insulin requirements of the mother fall considerably. Frequent blood glucose estimations and co-operation between the physician and dietitian are needed to ensure an uneventful return to the former diet and insulin dosage.

A final word of warning is necessary. It has already been indicated that glycosuria is not unusual during normal pregnancy, either because of a fall in the renal threshold for glucose, or through lactose appearing in the urine. But the finding of reducing substances in the urine of a pregnant woman should never be lightly dismissed as a normal phenomenon. Full clinical investigation to exclude diabetes is essential ; otherwise a preventable catastrophe may follow.

Surgery and Diabetes

" Infection makes diabetes worse and diabetes makes infection worse. Acute trauma makes diabetes worse." This dictum of Moore's (1959) summarises much clinical experience. He suggests that infection and trauma aggravate diabetes because they provide a stimulus to the production of adrenal steroids that antagonise the action of insulin. It is not so easy to provide an explanation of the adverse effect of diabetes on infection.

Any surgical operation, however minor, and the accompanying anæsthetic cause a metabolic stress (Chapter 47) which the diabetic is less well able to meet than the normal person. The stress is temporary and will not be aggravated by a mild hyperglycæmia, but an accompanying acidosis will prejudice normal recovery. The position is still worse if there is tissue wasting with much breakdown of fat and protein with the excretion of large amounts of potassium, phosphate and other intracellular electrolytes.

There are two general points to be kept in mind in treatment. First there is the necessity to provide an adequate supply of energy for the tissues. Moore's straightforward advice is : ' *Keep the glucose burning*.' Secondly, there is the need to be constantly on the *look-out for acidosis* and to introduce measures to counteract it promptly should it arise.

In practice there are two separate problems. The first is the management of a stabilised diabetic who has to undergo an operation at a time which can be chosen by the surgeon and physician. The second is that of a diabetic whose disease may not be well-controlled and who suddenly has to be operated upon because of trauma, acute sepsis or a major abdominal or other catastrophe, or one who is first discovered immediately prior to operation.

As both the severity of the diabetes and the extent of the operation will vary greatly, it is not possible to set out details of management. Each patient is an individual problem.

Elective surgery in a stabilised diabetic.—All diabetics must be admitted to hospital about three days before an operation, even a minor one. During this period the control of the diabetes can be checked thoroughly. Provided a diabetic goes to the theatre in a good condition, he is not likely to develop significant acidosis during the hour or so whilst he is in the hands of the surgeon and anæsthetist. In fact, hypoglycæmia is more likely to occur than acidosis. For this reason it is generally advisable to give no insulin immediately before operation. During the day preceding the operation the patient's usual diet and doses of insulin should be given. Presumably it will be possible to arrange for the operation to take place in the morning. The patient should receive no breakfast and nothing by mouth before operation. Before being transferred to the theatre the fasting blood sugar level should be determined. If this lies between 120 and 200 mg./100 ml. then no glucose or insulin need be given. If the level is below 120 then about 25 to 40 g. of glucose should be given intravenously, preferably in hypertonic solution, in order to prevent possible hypoglycæmia during the operation. No insulin is necessary. If the fasting blood sugar is over 200, which is infrequent, then some insulin will be required. About one-third of his usual total daily dose is indicated, preferably in the form of globin insulin, about one hour before the operation. This will not cause hypoglycæmia during the operation.

Recovery from the anæsthetic must be carefully supervised. The sooner the patient returns to his usual diet the better. The interval until this can be achieved may be anything from a few hours to several days (depending on the nature and severity of the operation). During this time it will be necessary to supply most of the energy requirements in the form of glucose, given either intravenously or by mouth, and to check the level of the blood sugar regularly. If all has gone well, a single determination of the fasting blood sugar each morning will suffice. If recovery is stormy, measurements may be necessary at 4-hourly intervals or even more frequently. Determination of the CO_2 combining power, pH and electrolytes will also be required. The insulin dosage will depend on these findings.

In addition to the investigations mentioned above, each specimen of urine passed by the patient must be tested for sugar and ketone bodies. If ketosis develops it is essential to take immediate steps to increase the metabolism of glucose by making suitable adjustment in the dose of insulin.

Diabetes and surgical emergencies.—Circumstances vary so much that it is impossible to consider them except in the most general way. The essentials are to maintain the oxidation of glucose by the tissues at a sufficient rate, and to combat acidosis and electrolyte disturbances if and when they occur. This can only be done effectively if the state of the diabetic control is assessed continuously and accurately. A laboratory service that can provide rapid results is thus an essential. As long as the surgical condition remains untreated and the ' metabolic stress ' continues, the diabetic condition is likely to get worse. Once the patient's surgical condition is under control he may be expected to respond promptly to the appropriate therapy for his diabetes.

PROGNOSIS

The prognosis in diabetes has improved steadily since the introduction of insulin ; but even with the use of insulin the average expectation of life is still a little less than that of a non-diabetic. It may be difficult to estimate the prognosis of an individual patient because so many variable factors have to be considered. Thus the child of parents poor in means and education, who is first seen in coma, obviously has a very different future compared with the middle-aged lady in easy circumstances who complains of nothing but a little thirst and irritation, and can afford the time and the means to follow precisely the diet prescribed for her.

General Prevention

The hereditary factor in diabetes is sufficiently strong to make it the doctor's duty to advise diabetics wishing to marry of the possible consequences to their children. If both parents have diabetes, the probabilities are that about half their children will develop the disease at some stage in their life. The risk is about half this if only one parent is affected but the other has a family history of the disease. If, despite this advice, diabetics decide to have children, they should know of their responsibility for keeping a careful watch for early symptoms of the disease in their offspring, whose future may depend on its prompt recognition.

Since little is known of the factors that initiate diabetes, nothing can be done to prevent it, except perhaps in obese patients. The incidence of diabetes among obese women who have previously given birth to infants over 10 lb. in weight is sufficiently high to justify recommending immediate weight reduction to the obese mothers of all such infants. It is likely that many other obese diabetics, both female and male, would never have developed the disease if their weight had always been normal, though this cannot be established with certainty. It is a reasonable guess, however, that if there were fewer fat people, there would be less diabetes. Its incidence declined markedly in several European countries during the food restrictions of the second world war. There are other good reasons for making it the duty of doctors and dietitians to wage relentless war on obesity (Chapter 27).

Finally, the prevention of the *complications* of diabetes offers a great opportunity for good medical practice ; there are few other chronic diseases in which the practice of preventive medicine can make so much difference to a patient's life.

CHAPTER 43

DISEASES OF OTHER SYSTEMS

IN most diseases of the locomotor, respiratory, nervous and hæmopoietic systems there is no evidence that dietary factors are of ætiological importance, and special diets are seldom required. Such general diseases, therefore, require much less consideration in a book dealing with nutrition and diet, and hence it is proposed to discuss them collectively in one chapter.

THE LOCOMOTOR SYSTEM

Diseases of the bones, joints, muscles and ligaments include a variety of disorders which are often loosely grouped together under the general heading of ‘ rheumatism.’ Rheumatic fever is not discussed in this chapter because, although in the acute stage it may have a transitory effect on joints, its main effects are usually on the heart.

The cause of rheumatic disorders is seldom simple and often obscure. They differ from each other widely in their ætiology, pathology and clinical course. They are often chronic, painful, disabling illnesses from which there is frequently little relief except by palliative measures such as physiotherapy and the prescription of analgesic drugs and corticosteroids. It is not surprising that numerous patients and their doctors have resorted to every possible method of treatment, including special diets. Various dietary regimes have been prescribed in the past ; it must regretfully be stated, however, that these have been founded on false hopes and mistaken theory. For a time it was widely believed that ‘ rheumatism ’ was due to an accumulation of acids in the body ; efforts were made to avoid ‘ acid ’ foods, or to prescribe a diet that would keep the urine permanently alkaline. However, there is no evidence to associate rheumatism with ‘ acidity,’ which is an outworn notion as explained at the end of Chapter 10. A diet low in meat was often recommended to maintain an alkaline urine and also because of the erroneous belief that rheumatism is due to disordered purine metabolism, which is only the case in gout. Particular foods were often banned in the belief that they were the allergic cause of the disorder. Chapter 46 explains how tenuous the evidence is for attributing any disease to allergy unless a definite allergen has been demonstrated.

Before further considering dietary measures in the treatment of locomotor disorders it may be of value to give a brief classification of them.

Classification

1. *Diseases in which the chief symptoms are often referred to the joints.*
    - Rheumatoid arthritis.
    - Osteoarthritis.

Ankylosing spondylitis.
Acute rheumatic fever.
Infectious arthritis (*e.g.* in gonorrhœa, tuberculosis, dysentery).
Neuropathic arthritis (*e.g.* in syringomyelia, tabes dorsalis, diabetes mellitus).
Gout.

2. *Diseases of connective tissue* (*collagen diseases*).
    Non-articular rheumatism.
    Rheumatoid arthritis.
    Disseminated lupus, dermatomyositis, scleroderma.
3. *Diseases of muscle.*
    The myopathies (muscular dystrophies).
4. *Diseases of bone.*
    These have been discussed in Chapter 30, in so far as they are related to nutrition.

There is no satisfactory evidence to show that dietary deficiency plays any role in their causation or that diet is of specific value in their treatment. It was at one time believed that injections of vitamin E were of value in the treatment of the myopathies, but this view is no longer accepted by most physicians to-day. Many of the diseases in the above list are rare, but there are three disorders of the locomotor system, often referred to collectively as the chronic rheumatic diseases, which are so common and so frequently a cause of disability that some further comments are needed on their ætiology, clinical course and treatment, with special reference to dietetic measures.

THE CHRONIC RHEUMATIC DISEASES

The principal members of this group are rheumatoid arthritis, osteoarthritis and non-articular rheumatism. The chronic rheumatic diseases account for a very important proportion of temporary or permanent disablement in temperate climates. The rheumatic group of diseases is second only to bronchitis in men and holds first place among women as a reason for seeking medical advice. A recent survey (Lawrence, 1961) suggests that approximately 1,740,000 of the population of Great Britain have ' probable ' or ' definite ' rheumatoid arthritis, and that some 3,700,000 persons over the age of 65 are disabled to some extent by osteoarthritis.

In general practice it has been estimated that about 10 per cent. of practitioners' work is devoted to the diagnosis and treatment of various forms of rheumatism. Finally, the pain and misery endured by those affected must never be forgotten.

For these reasons it is most important that every effort should be made to elucidate the cause of the chronic rheumatic diseases and to discover therapeutic measures for their prevention and cure.

Rheumatoid arthritis

Rheumatoid arthritis occurs in people of all ages. The peak incidence in both men and women is approximately at the age of 40. It occurs in women at least three times as frequently as in men, for reasons not known. It is mainly a disease of temperate climates which are associated with cold and damp. Heredity may also be of importance. The presence in the serum of abnormal globulins with the characteristics of antibodies in a high proportion of patients has led to the idea that rheumatoid arthritis may be associated with a derangement of the immune response to exogenous antigens, or to antigens derived in part at least from the patient's own tissues. It is commonly stated that it occurs most often in people of asthenic build. This is particularly noticeable when the disease starts in women between the ages of 20 and 40, but when it begins at a later age, constitutional factors are less apparent. Many middle-aged female patients are fat and flabby. Nevertheless there is no evidence that the dietetic habits of patients suffering from rheumatoid arthritis are abnormal. The fact that they are often underweight is more frequently the result, rather than the cause, of the disease.

Clinical features.—The onset is usually insidious. Muscular stiffness develops first and is followed later by pain and swelling of many joints, starting frequently with the small joints of the hands and feet. During the active stage of the disease the patient suffers from general malaise and fatigue ; fever is often present and the appetite is poor. In such patients loss of weight usually occurs. There is frequently some degree of anæmia ; the erythrocyte sedimentation rate is often increased and the plasma protein pattern altered ; the blood level of ascorbic acid may be low.

Treatment.—The successful treatment of rheumatoid arthritis, ankylosing spondylitis, and the collagen diseases depends on the co-ordinated efforts of the physician, orthopædic surgeon, physiotherapist, occupational therapist and social service worker. The programme of treatment must be carefully co-ordinated to meet the needs of each individual case. All factors likely to have an adverse influence on the patient must be dealt with, and recommendations as to future activity must be based on an accurate knowledge of functional capacity. These ends can best be achieved in special units devoted to the study and treatment of the chronic rheumatic diseases. Although *diet* has no specific curative value, common sense dictates that an attempt should be made to correct anæmia and loss of weight by diet and other measures.

The essential task is to improve the state of nutrition, and to this end the whole art of the dietitian may be needed. Any foods that will tempt the patient to eat may be tried, but in general those rich in protein, calcium and ascorbic acid should be offered first. Additional vitamin and mineral concentrates are often prescribed, although their value is doubtful. A high caloric diet may be required to restore loss of weight. Marked clinical improvement is often associated with a better state of nutrition.

Osteoarthritis

Osteoarthritis is characterised by degeneration of the articular cartilage and the formation of bony outgrowths at the edges of the joints. A generalised form of the disease commonly occurs in middle-aged women in whom the small joints of the fingers, the carpometacarpal joint of the thumb and the interfacetal joints of the spine are particularly affected. The more localised form, in which only one or two of the larger joints are involved, occurs amongst elderly people of both sexes. The condition may appear at any age in a joint which has been damaged by disease or injury. There is no impairment of general health.

Ætiology.—Osteoarthritis arises as a result of an exaggeration of normal ageing in the joints. When one joint is particularly affected a history is frequently elicited of an injury to that joint some years before. Malalignment following fractures of the long bones frequently gives rise to osteoarthritis in adjacent joints. Symptoms are prone to develop in the weight-bearing joints or those joints subjected to excessive strain at work. In most patients symptoms do not appear before the age of 50. Males and females are both affected, but the small peripheral joints are usually involved only in women. It has been suggested that in those cases in which many joints are involved there may be an inherited defect of the articular cartilage.

Clinical features.—The joints most frequently involved are those of the spine, the hips, knees, elbows, and in women the terminal joints of the fingers. The symptoms are gradual in onset. Pain is at first intermittent and of an aching character, appearing especially after the joint has been used, and relieved by rest. As the disease progresses, movement in the affected joints becomes increasingly limited, at first by muscular spasm and later by the loss of joint cartilage and the formation of osteophytes. General health is usually excellent and the blood sedimentation rate is within normal limits. Patients are frequently obese, and other degenerative disorders, such as atheroma and essential hypertension, may co-exist.

Treatment.—The pathological changes in osteoarthritis are irreversible, but much can be done to alleviate the symptoms. For this purpose, rest, graduated physical exercises and physiotherapy, including hydrotherapy, are of particular value. Analgesics must be prescribed according to the patient's needs. In selected cases orthopædic operations are indicated. *Diet* has a limited, though useful, part to play in treatment. There is no evidence that a deficiency of any known nutrient is responsible for the primary defect, the degeneration of the articular cartilage. On the other hand obesity, by placing an extra strain on the joints, may hasten the onset. In addition, once the disease is established, pain and joint deformity reduce the patient's capacity for physical exercise and this renders him more liable to become obese unless he takes the necessary dietary precautions. Hence the prevention and correction of obesity as described in Chapter 27, is a valuable aid in management.

Non-articular rheumatism

'Non-articular rheumatism,' 'muscular rheumatism' and 'fibrositis' are terms which describe a number of conditions characterised by pain and stiffness, often of sudden onset, affecting mainly the neck, shoulders, back and gluteal regions. Usually no cause can be found, and related joints show no radiological abnormality. Not infrequently, areas of acute tenderness can be demonstrated in the soft tissues. Pressure on these reproduces the pain felt by the patient. Systemic symptoms are absent and laboratory tests negative. The symptomatology varies according to the structures involved, and there must be few people in Great Britain who reach middle age without experiencing one or more attacks of this nature.

Ætiology.—Exposure to cold and damp, excessive or unaccustomed muscular activity, injury to muscles and tendons, poor posture, infections, metabolic and endocrine disorders are factors which individually or collectively have been held responsible. The opinion is now widely held that muscular pain and stiffness arise most commonly as a result of strain or injury to ligamentous or articular structures. Thus most cases of brachial neuralgia, lumbago and sciatica result from degenerative changes in the intervertebral discs, either from prolapse of the nucleus pulposus or from narrowing of the intervetebral foraminæ, leading to pressure on spinal nerve roots.

Clinical Features.—The presenting symptoms are commonly pain and stiffness which are often acute. The patient may be severely incapacitated. In the more chronic stage pain is felt most often after rest and improves with moderate activity. Palpable nodules are seldom present. Acutely tender points, sometimes referred to as 'myalgic lesions' may be located, pressure on which reproduces the pain complained of by the patient. Muscular spasm may be marked and movement limited. There is no evidence of systemic disturbance. The features in each case will depend on the site of the lesion.

Treatment.—In the acute attack of muscular rheumatism such as lumbago, rest in bed is essential, together with heat to the effected part and analgesics in ample amounts. At a later stage physiotherapy (heat, massage and graduated exercise) is essential. In cases with lesions of the intervertebral disc causing root pressure, operation should be considered. *Diet* has no specific part to play in curative treatment but if the patient is obese a reduction in weight may be of value in the relief of symptoms.

Summary

No specific diet is needed for the treatment of patients suffering from the chronic rheumatic diseases. Provided they take a well-balanced diet no dietary supplements of vitamins or minerals are required. For those patients who are underweight or overweight respectively the dietetic measures discussed in Chapters 27 and 48 are obviously applicable. The only member of this group of diseases that has a traditional relation to diet and may be helped by dietetic means is gout.

GOUT

Definition.—Gout is a chronic disease due to an inborn error of purine metabolism. It is characterised by recurrent episodes of acute metabolic disturbance, associated with a severe local arthritis. It may ultimately lead to crystalline deposits of sodium urate forming in the tissues, especially in cartilage and synovial membranes. A useful symposium on gout has been edited by Talbott (1957).

History.—Gout was familiar to the Greek and Roman physicians of antiquity. Many famous men have suffered from it, including Newton, Darwin, Franklin, Milton, Gibbon, Dr Johnson, the Pitts (both of them) and Louis XIV. The great physician Sydenham wrote in 1663 his classic description of the disease from which he was himself a life-long sufferer.

The specific value of the root of the autumn crocus (*Colchicum autumnale L.*) in the relief of acute attacks of gout was discovered in the course of the eighteenth century. The plant was introduced into America for this purpose by Benjamin Franklin. It contains the alkaloid colchicine which is still a most valuable drug in the treatment of gout.

In 1848 Sir Alfred Garrod demonstrated an excess of uric acid in the blood of gouty patients.

Ætiology—HEREDITY.—It used to be fashionable for a patient with gout to attribute his disease to his grandfather's port-drinking habits. Although grandpapa may have kept a good cellar and perhaps suffered in consequence, there is little doubt that his predisposition to the disease was not due to port-drinking but to the inheritance of an abnormality in purine metabolism as discussed below. About three-quarters of all cases of gout have a family history of the disease. The family trait has been established still more firmly in recent years by the demonstration that near relatives of gouty patients frequently have an elevated level of uric acid in the serum, indicating an abnormality of purine metabolism, although few of the male relatives and usually none of the females have the clinical features of gout. The basic abnormality of purine metabolism is apparently inherited through a single, dominant, non-sex-linked gene. But it remains a mystery why only a minority of those who have this defect ultimately develop gout. Clearly certain precipitating factors must be involved. The disease may be compared with acute porphyria, in which near relatives of the patient, though in obvious health, may show the same underlying defect in porphyrin metabolism by excreting excessive amounts of porphyrin in the urine. But the cause and nature of the metabolic storm that changes this benign inherited defect into a dangerous and sometimes fatal disease remains obscure.

RACE.—Gout probably afflicts all races, but is perhaps most common in people of English or German descent.

FOOD; QUANTITATIVE AND QUALITATIVE ASPECTS.—It has been recognised since the earliest times that large, enjoyable meals and the consumption of alcoholic drinks were often the prelude to an attack of gout. Doctors have long imposed some sort of dietary discipline on their gouty patients, sometimes of the most bizarre kind. A rational basis for such dietetic advice was apparently achieved when, about 100 years ago, Garrod demonstrated that gout was characterised by an increase in uric acid in the blood. For a time it was assumed that this uric acid was derived directly from the diet, and that preventive and curative treatment should be based on the avoidance of meat foods. To-day it is clear that the nucleoproteins derived from the diet contribute, at most, only 50 per cent. of the uric acid present in the blood of normal people, and cannot account for the high levels found in gout.

Nevertheless experience has shown that an acute attack of gout frequently follows a bout of eating and drinking. Heavy wines such as port, Madeira or Champagne are said to be more liable to produce an attack than light wines, such as hock or white Bordeaux. Likewise ' poor man's gout ' is thought to occur more frequently in beer drinkers than in spirit drinkers, though teetotallers may also be afflicted. Some patients attribute their attacks to a single specific article of food to which they appear to be hypersensitive, such as asparagus or strawberries, which contain insignificant amounts of purines. At one time food allergy was believed to be of great ætiological importance in the causation of gout but this is no longer generally accepted. Perhaps more significant than the quality of the food consumed preceding the acute attack is the total quantity. Although the doctor may find it convenient to agree with the patient that some single unaccustomed food at the banquet of the night before was responsible, in fact it seems more likely that an unusually large and rich meal is the trigger that sets the metabolic storm in those predisposed to it. The alcoholic drinks included in the banquet may well be a contributing factor.

SEX.—Ninety per cent. of cases of gout are males. They often inherit the predisposition to it through their mothers, who themselves were free from the disease. The relative immunity of the female to gout is perhaps due to the influence of the sex hormones. Women seldom develop gout before the menopause. In women with gout the level of uric acid in the serum is usually higher than in male cases, suggesting that a more severe defect in purine metabolism is necessary to produce the clinical disease in women.

AGE.—Gout may begin at any age between puberty and senescence, but it starts most commonly between the ages of 40 and 50.

PSYCHOLOGICAL FACTORS.—To judge by the history of gout, it afflicts men of high intelligence more often than the stupid. Sydenham said that it " kills more Rich than Poor, more Wise than Fools."

PRECIPITATING FACTORS.—As with diabetes mellitus, the onset of the metabolic storm that precipitates an acute attack is often related by the patient and his doctor to some unusual experience or stress. In gout there is better circumstantial evidence than in diabetes that stress is the precipitating factor. Exposure to cold, undue fatigue, trauma, a surgical operation or, above all, gastronomic excesses, may be the prelude to the first and all subsequent attacks of gout.

A patient of ours describes most graphically how, in his forties, he enjoyed 10 days of pleasurable gastronomic experience on a Mediterranean cruise. Stepping off the dock at Naples he was unexpectedly smitten with a frightful, stabbing pain in his big toe. Years later he developed typical gouty deposits of sodium urate in his ears, feet and hands.

Epidemiology.—To judge from the medical literature of the last three centuries, gout, like stone in the bladder (p. 591), is now much rarer than it used to be. Undoubtedly this is due to the fact that it was at one time a fashionable disease ; any kind of arthritis (especially rheumatoid) was likely to be diagnosed as gout, just as any skin condition was attributed to the pox (syphilis) or scurvy. If true gout is now rarer than it used to be, it is because of the decline in the Sin of Gluttony, which our ancestors regarded with good reason as an important predisposing cause.

Chemical pathology.—Gout occurs in those predisposed to it. This predisposition is indicated by an elevated level of uric acid in the serum. The normal level lies between 3 and 6 mg./100 ml. (Buzard *et al.* 1952) and is generally lower in women than in men. Although patients with chronic gout may sometimes be found to have a level within the normal range in a random specimen of blood, a subsequent test will usually show an elevated figure, *i.e.* above 6 mg./100 ml. in male patients and above 7 mg./100 ml. in the very rare cases of gout occurring in post-menopausal women. It may be as high as 14 mg./100 ml.

This high uric acid content of the serum is not a specific feature of gout ; it occurs in a variety of other diseases, notably in chronic renal failure, leukæmia and polycythæmia ; hence raised serum uric acid is certainly not the cause of gout, nor certain evidence of the disease. Nevertheless it is a regular feature and, when combined with the characteristic clinical signs, establishes the diagnosis.

The cause of the raised serum uric acid in gout has been much disputed. In theory it might be due to (1) diminished excretion of uric acid, (2) diminished catabolism of uric acid, (3) increased production of uric acid, or a combination of any of these.

1. There is no evidence that the excretion of uric acid is impaired in patients with gout, except temporarily during the oliguria of an acute attack (see below) or permanently when chronic renal failure develops as a complication of the disease.

2. Before considering the catabolism of uric acid, it is useful to consider its origin in the body. Studies making use of isotopic nitrogen indicate that the total ‘ miscible pool ’ of freely exchangeable uric acid in the body fluids is normally about 1 g. The sources of this pool are twofold :

exogenous and endogenous. The exogenous source is the diet. A good mixed diet of Western type contains purines sufficient to provide 0·5 to 1 g. uric acid/day. About 20 per cent. of the dietary purines is destroyed in the process of digestion ; but the greater part goes to form uric acid in the body's miscible pool. The second (endogenous) source is the purines that the body makes for itself in the course of the synthesis of its own nucleoproteins. With the aid of isotopes it has been shown that the body can make purines from the simplest of compounds, such as glycine, or formic acid and ammonia derived from the general metabolic pool of products from the catabolism of the proteins, carbohydrates and fats of the diet. The extent of endogenous uric acid production can be judged by the fact that on a purine-free diet the body excretes about 0·5 g. uric acid/day.

Normally about half the uric acid in the body comes directly from the diet and the other half from purines synthesised within the body. The amount of uric acid destroyed in the body is small, even in normal people. With the aid of uric acid labelled with ^{15}N, it has been concluded that less than one-fifth of the miscible pool of uric acid is normally catabolised ; the greater part is ultimately eliminated in the urine. Gouty patients are not any different in this respect from normal people ; a failure to destroy uric acid through the necessary catabolic pathways is not the explanation of gout.

3. In gout the miscible pool of uric acid in the body is increased and may be as much as 30 g. This offers a simple though not wholly satisfactory explanation for the precipitation of crystalline deposits of sodium urate (which is only slightly soluble in water) in the joints and elsewhere in the body. It is now agreed that the chief source of this increased pool is an excessive endogenous production of purines. Since this production requires only the simplest of raw materials, it is not dependent on the supply of any single class of nutrient in the diet. In summary, diet as a source of exogenous purines is only of secondary importance in the ætiology of gout. The primary defect lies in the gene that permits excessive endogenous purine synthesis.

Morbid anatomy.—In chronic gout crystalline deposits of sodium urate develop in the soft tissues, especially in cartilage and synovial membranes. These have a predilection for certain sites (see below under clinical features). They may be found also in the pyramids of the kidneys ; this may contribute to the chronic renal failure which was often a terminal complication. Small urate stones (gravel) are sometimes found in the renal pelvis and ureters.

Clinical features.—(1) THE ACUTE ATTACK.—The first attack is often a dramatic and alarming experience in the patient's life. He has usually enjoyed good health until his forties, when, following an exceptionally good meal or some other stress he suddenly experiences (often in the middle of the night) an acute, agonising, stabbing pain in one joint, generally of the big toe. The joint selected for attack is thought to be determined by its susceptibility to minor injury ; the big toe is easily stubbed, or injured by an ill-fitting shoe. The wrists, the ankles and the knees are much less common sites. On the whole, it is the peripheral rather than the central joints that are affected, with the spine practically immune. The joint is swollen and tender ; acute pain occurs on the least movement. At the start the overlying skin is tense, red and shiny, and later may show œdema.

The attack is often preceded by a diuresis, with an increased elimination of sodium and uric acid ; but when the attack begins the urine becomes scanty and highly coloured. Associated with the onset of acute arthritis there is usually a profound systemic upset with anorexia, malaise, fever, polymorphonuclear leucocytosis and a marked increase in the erythrocyte sedimentation rate (ESR), all of which may suggest an infection. The uric acid in the serum rises. The patient is often exceedingly irritable and bad tempered. With proper treatment the acute attack subsides in about 2 days.

(2) CHRONIC GOUT.—With proper treatment (see below) there may be no further attacks for years, but if the disease is neglected they tend to recur with increasing frequency and last longer. Finally the disease passes into a phase of chronic, persistent, though generally less painful arthritis of several affected joints. It is during this phase that *tophi* begin to appear. These are crystalline deposits of sodium urate which develop in the lobes of the ear, at the base of the big toe, in other toes or fingers, in the olecranon bursa above the elbow, or in tendon sheaths on the back of the forearm. A gouty tophus may vary in size from a pin-head to that of a golf ball. It is painless between acute attacks. The overlying skin may ulcerate and the chalky sodium urate breaks out on the surface. The ulcers are slow to heal but seldom become infected. At least one university lecturer has been able to write on the blackboard with the urate from his own knuckles. When the tophi develop in joints they erode the neighbouring bone and appear on radiological examination as clear, punched-out areas, since sodium urate is not opaque to X-rays.

Complications.—Without adequate treatment, patients with chronic gout are liable to develop chronic renal failure in later life. This may lead to retention of uric acid in the body, with aggravation of the disease. Renal colic, due to the passage of urate stones or gravel in the urinary tract, is an occasional complication.

Diagnosis.—Acute attacks of gout need to be distinguished from acute rheumatic fever, acute rheumatoid arthritis and especially from infective or suppurative arthritis. In the chronic stage it may be mistaken for osteoarthritis. The level of uric acid in the serum should always be estimated in case of doubt. If it is elevated above normal levels, gout is the probable diagnosis. The characteristic biochemical feature of gout is a level of uric acid in the serum proportionately higher than that of other nitrogenous products. The radiological appearance of the joints in gout is not specific, and must be distinguished from the other diseases that produce localised rarefaction of bone. A useful aphorism in the diagnosis of systemic disease associated with arthritis is ' in case of doubt, think of gout.'

Treatment

Treatment must vary according to the individual. Some patients, after a single acute attack, remain in a state of natural remission for years without any further disability. It is obviously poor practice to burden such a patient with dietary restrictions and the prescription of drugs. There are other cases, however, in which the attacks are so frequent and severe, sometimes with little or no remission between them, that only regular and strict medical supervision can render the patient's life tolerable. In between these extremes are cases in which attacks develop every few weeks or months.

Principles of dietetic treatment.—(1) CALORIES.—Many patients who first develop gout in middle life are overweight. Obesity predisposes to gout just as much or even more than it does to diabetes mellitus. The physicians of a previous generation wisely advised their patients to avoid civic banquets. A simple weight-reducing diet is a most important means of preventing attacks of gout in overweight patients. Even gouty tophi may regress and disappear on such a regime. This regression has often been ascribed to drugs that happen to have been administered at the same time. The effect of such drugs cannot be correctly assessed unless the nature of the patient's diet, and the response of his weight to it, is fully recorded.

(2) FAT.—Numerous observers have noted that a diet rich in fat reduces the urinary excretion of urate in gouty patients ; accordingly a reduced intake of fat in the diet is indicated. Precisely why fats have this effect on uric acid excretion is not clear.

(3) PURINES.—Elaborate dietary regimes have been recommended in the past for gouty patients with the idea of eliminating, so far as is possible, all exogenous sources of purines. Meticulous attention to the purine content of every foodstuff is unwarranted in view of the knowledge that dietary purines are responsible only for a part of the excess uric acid that accumulates in gout. Nevertheless a patient having an acute attack or one who suffers from frequent attacks or has chronic gout should avoid any unnecessary dietary additions to this metabolic burden. The foodstuffs rich in purines are those that have a high content of nucleated cells containing nucleoproteins. It is easy to divide foodstuffs into three categories on this basis, as in Table 43, 1.

(4) DRINK.—The association of alcohol with an attack of gout has already been described in the section on ætiology. The essential dietetic principle to be followed is moderation. Reasonable amounts of light wines, spirits and ales may be allowed unless it is shown by trial and error that they precipitate attacks. Coffee and tea used to be forbidden because these contain caffeine which is a methyl purine ; but since it is not

TABLE 43, 1. *Foodstuffs classified according to their content of purines (modified from Hench,* 1941)

High (150 to 1000 mg. purine/100 g. edible portion)	Moderate (75 to 150 mg. purine/100 g. edible portion)	Low or absent (below 75 mg. purine/100 g. edible portion)
To be avoided— Fish roes Whitebait Sprats Sardines Smelts Herring Sweetbreads (pancreas or thymus) Liver Kidney Heart Meat extracts and gravies	*One portion only at each meal*— Meats Chicken or other birds White fish	*To be taken* ad lib.— Milk and milk products Eggs Cereals* Vegetables Fruit Sugar

* Whole and undermilled cereals may contain considerably more.

converted into uric acid in the body, there is no theoretical or practical justification for this advice.

Management of the diet.—(1) DURING AN ACUTE ATTACK.—During the 2 or 3 days that an acute attack lasts the patient usually has a poor appetite, with wind, vague abdominal distress and sometimes hiccough. He has little inclination to eat. Clearly it is unrealistic to prescribe for him any precise diet for so short a period, and in any event it is likely that he will reject much of what is offered to him. His own preference should be consulted provided the dishes selected are made from the purine-poor foods listed in column 3, Table 43, 1, *e.g.* eggs, milk, milk products, cereals, fruit and vegetables. A small helping of white fish may be allowed. It is wise to avoid all superfluous fat because it is liable to hinder the excretion of uric acid.

The patient should be encouraged to drink as much fluid as possible, 6 pints (3 *l.*) daily, in order to promote the excretion of uric acid. Here, again, the patient's preference may well be consulted; mineral water, barley water, lemonade or milk may all be given. All alcoholic drinks should be forbidden.

Sodium bicarbonate in a glass of water between meals may help to relieve gastric discomfort; at the same time it will aid the production of an alkaline urine in which the uric acid excreted will be more readily soluble and therefore less likely to form calculi. The patient should not be given a purge, particularly if he is being treated with colchicine (see opposite), since the subsequent loose motion may wrongly suggest an excessive dosage of this drug. If constipation causes discomfort it can be relieved with an enema.

(2) BETWEEN ATTACKS AND IN CHRONIC GOUT.—When attacks tend to

occur every few weeks or months, or when a chronic gouty state has become established, dietetic treatment should be advised.

Despite the scepticism of experienced physicians from Sydenham onwards about the ultimate value of any dietetic measure in halting the progress or preventing the complications of gout, the modern view is more sanguine. Previous failures in dietetic treatment have perhaps been due to too much preoccupation with the *quality* of the diet, aiming at avoiding all foods that give rise to uric acid. If more attention had been paid to the *quantity* of food prescribed, better results might have been achieved. As has been said already, patients who contract gout for the first time in middle life are often overweight. The first aim, therefore, should be to reduce them and the dietary treatment differs in no way from that of ordinary obesity as described in Chapter 27, except that all purine-rich foods should be avoided. Once the patient has achieved a satisfactory weight loss, the degree of subsequent dietary discipline must be determined by trial and error.

Patients with chronic gout or those who have acute attacks at fairly frequent intervals should (*a*) learn the list of purine-rich foods in column 1, Table 43, 1 and avoid them ; (*b*) limit their consumption of meat, fish, game or chicken (column 2) to one small helping at lunch and supper ; (*c*) eat as much as they wish of milk, eggs, cheese and other foods in column 3 ; (*d*) be sparing in their use of fat (butter, margarine, cream) ; (*e*) avoid alcoholic excess ; (*f*) drink plenty of water ; (*g*) avoid putting on weight.

Drugs.—(1) COLCHICINE.—Of all drugs, colchicine has pride of place as a specific in the treatment of gout. This alkaloid, isolated more than 100 years ago from the root of the autumn crocus, aborts the acute attacks and, if subsequently taken regularly, reduces their frequency. Its precise mode of action is still uncertain. It does not influence the urinary excretion of uric acid. Following the pioneer research of Professor A. P. Dustin of Belgium, it is now known that colchicine arrests mitosis in the cells both of animals and plants. Ludford (1945) and Cook and Loudon (1952) give two useful reviews with full references to the extensive literature on this interesting subject. Hence it seems possible that the efficacy of colchicine in gout is due to its power of arresting cell division throughout the body. It is even possible that the essential inherited trait in gout is a tendency to too frequent cell division.

In an acute attack colchicine should be given in adequate doses (*e.g.* 0·5 mg. 2-hourly) until pain is relieved or diarrhœa or vomiting occurs. The maintenance dose suitable for chronic gout varies from case to case.

(2) PHENYLBUTAZONE.—Phenylbutazone is another valuable drug for the treatment of an acute attack of gout. It should be given in a dose of 0·4 g. followed by 0·1 g. every 4 hours until pain is relieved ; but because it can cause serious side-effects its use should be restricted to acute cases that fail to respond adequately to colchicine. It should never be used for the day-to-day treatment of chronic cases. Although phenylbutazone

causes a great increase in excretion of uric acid, it is chiefly for its remarkable analgesic and anti-inflammatory effects that it is valuable in the acute attack.

(3) Other drugs.—Various drugs have been introduced from time to time to aid the urinary excretion of uric acid and thus to reduce the miscible pool of the acid and dissolve the tophi. All of these apparently act by impairing the power of the renal tubule to reabsorb uric acid from the glomerular filtrate. The first of such drugs to have widespread use was cinchophen, but it has now been generally abandoned because it is a severe liver poison and occasionally gives rise to fatal toxic hepatitis. At present the most popular drugs of this class are probenecid (Benemid in the U.S.A.) in doses of 0·5 g. three or four times daily, and anturan (a pyrazolidine derivative) in doses of 0·2 to 0·4 g. daily. The effective dose of these drugs is often near the toxic dose ; nevertheless they are of great value in severe cases of chronic gout. If given over a period of months the blood uric acid may return to normal, tophi may disappear or become reduced in size and the dangers of serious renal and arthritic damage may be reduced. There is now considerable evidence that the continuous administration of 1 mg. of colchicine and 1 g. probenecid daily in divided doses may be of greater value in reducing the number of acute attacks in moderate or severe cases than the use of probenecid alone.

(4) Hormones.—It has been shown that both cortisone and corticotrophin can be used to control acute gout. Corticotrophin is the more effective, but must be given in conjunction with colchicine if relapse on withdrawal of the hormone is to be avoided. This method of treatment is not recommended for routine use, as only exceptional cases will fail to respond either to colchicine or phenylbutazone.

(5) Analgesics.—During the acute attack the patient gets little rest from pain in the affected joint which is always worse at night. Codeine, pethidine or some other analgesic may be required while awaiting the effects of colchicine or phenylbutazone.

Spa treatment.—In patients with chronic gout a visit to a spa once or twice a year may do much to relieve stiffness and rigidity, and prevent deformities in joints that have long been afflicted with the disease. It should be realised, however, that hot baths and vigorous massage may precipitate a relapse in a patient newly recovered from an acute attack of gout. In addition to physiotherapy and hydrotherapy the good spa physician employs diet and drugs on the lines discussed above.

Summary.—As in all chronic diseases the proper management of gout needs sensible supervision by a physician. Apart from attendance when summoned to relieve the acute attacks, the doctor should pay regular attention to the patient's weight and to his requirements for drugs. Kindly reminders may be needed about the dietetic principles mentioned above, and the importance of avoiding a repetition of the particular environmental or gastronomic situation that precipitated the previous attack.

THE RESPIRATORY SYSTEM

The main causes of disease in the respiratory system are (*a*) infection; (*b*) allergy; (*c*) vascular accidents; and (*d*) malignant disease.

Infection.—This is by far the most important cause of disease in the respiratory tract, *e.g.* coryza and sinusitis in the upper passages, tracheitis, bronchitis, bronchopneumonia and influenza in the bronchial tree and lobar pneumonia and tuberculosis in the lungs.

Infection of the respiratory system may be caused by a virus, as in the case of coryza, influenza and virus pneumonia, or by bacteria, as in bronchitis, bronchopneumonia, lobar pneumonia and tuberculosis.

The complex problems of the part which nutritional deficiency plays in preventing infections in general are discussed in Chapter 56, and also the contribution which diet makes to helping the patient to overcome an infection once it has been acquired. The conclusion reached is that although diet may be important in some instances, factors other than nutritional are usually of greater significance. In respiratory disease these include: (*a*) *immunity*, which may be natural or acquired by contact with small amounts of virus or bacteria, or by artificial vaccination (for example with B.C.G.); (*b*) *the risks of infections*, which are increased by overcrowding, poor houses, bad air hygiene in shops, factories, schools and places of entertainment; (*c*) *chemotherapy and antibiotics* which are of great therapeutic importance. This was clearly shown in a controlled experiment carried out in Madras. Two groups of Indians with severe pulmonary tuberculosis, one living in ideal institutional conditions in hospital, and the other living at home in slum dwellings and eating a very poor diet, did equally well on chemotherapy (p. 784). In Chapter 45 specific dietary instructions are given for the treatment of such febrile illnesses.

Allergy.—Certain respiratory diseases are allergic in origin. The most obvious example of this is hay fever. Another disease in which allergy plays an important role is bronchial asthma. Besides inhaled dust or pollen, ingested foods such as eggs, milk, wheat, shell-fish, etc., can be responsible for asthma. The detection of a food allergen and its subsequent exclusion from the diet may be an important factor in the treatment of asthma. The role of food allergy in the causation of disease is discussed in Chapter 46.

Vascular accidents.—Thrombosis or infarction of the lung is not so frequently a cause of death or serious disability as when they involve the heart or nervous system. Nutritional factors play no part in the ætiology except in so far as they contribute to underlying atherosclerosis of the arteries (Chapter 40), nor is any particular diet of value in the treatment of thrombosis. Anticoagulant drugs and antibiotics have, however, made an important contribution to the prevention and treatment of pulmonary infarction.

Malignant disease.—Malignant disease of the bronchial tree and lungs has greatly increased in frequency in recent years. Tobacco smoke and pollution of the atmosphere with smoke and fumes are widely believed to be of ætiological importance. There is no evidence that nutritional factors play any part in the causation of bronchial carcinoma or that dietetic treatment influences the course of the disease.

THE NERVOUS SYSTEM

The brain is responsible for about one-fifth of the basal matabolism and its need for glucose and oxygen has long been recognised. Nitrogenous and fatty material is also required for the growth and regeneration of myelin sheaths and axis cylinders and for the enzyme systems needed for cellular metabolism. Sodium and potassium and other electrolytes are required for the maintenance of the cerebral spinal fluid and the fluid content of nerve cells. Lastly certain vitamins, especially those belonging to the B complex, must be available in adequate amounts since they are essential for the metabolism of carbohydrate which plays such a predominant role in the metabolism of the nervous system.

In considering the problem of nutritional deficiencies in patients suffering from neurological diseases or psychiatric disorders, it should be clearly realised that such deficiencies are much more frequently the result rather than the cause of these diseases or disorders. Neurological diseases in which malnutrition is of primary ætiological importance are the nutritional encephalopathies and neuropathies associated with pellagra (nicotinic acid deficiency), beriberi (thiamine deficiency), Wernicke's encephalopathy and Korsakoff's syndrome (thiamine deficiency), and subacute combined degeneration of the cord (vitamin B_{12} deficiency). The reader is referred to Chapter 33 for a description of the clinical features and treatment of these diseases and other primary nutritional disorders affecting the brain, spinal cord and peripheral nerves.

The same pathological processes which affect other systems of the body are encountered in the nervous system ; for example, acute and chronic infections, vascular disease and neoplasms. In addition there are many diseases, the nature of which is not known. Examples of these are degenerative disorders such as motor neuron disease, and demyelinating disorders such as disseminated sclerosis.

In organic diseases nutrition may be affected secondarily in a variety of ways. Thus, difficulty in taking sufficient nourishment is of particular importance when paresis or paralysis of the neuromuscular process of swallowing is involved. Increased expenditure of energy may result when movements are made difficult by weakness or paralysis of limbs. Wasting of muscles and other tissues tends to occur if the patient is bed-ridden. When mental deterioration is associated with physical handicaps, and especially if these disorders are present in an elderly person living alone, the resultant anorexia and difficulty in feeding may be a potent cause of malnutrition and undernutrition.

Nutritional disorders, leading to subnutrition which may be extreme, may develop both in children and adults (anorexia nervosa, p. 523) as a result of emotional factors (hate, fear, lack of love and other stress-producing situations). More rarely obesity may develop as a result of capricious or voracious appetite (p. 382). Likewise, patients with psychotic illness are liable to suffer from malnutrition consequent on depression, stupor, agitation or mania.

Sufficient has been said to emphasise the need for physicians in charge of patients with neurological disease or psychiatric disorders to be constantly aware of the real danger of malnutrition being the cause or the result of these illnesses. For the detection of nutritional deficiency, a careful history of past and present eating habits and food consumption must be taken, and this must be followed up by a full clinical examination designed particularly to detect the earliest signs of malnutrition. The reader is referred to Part III of this book which deals with the primary nutritional diseases and in particular to Chapter 37 in which a description is given of the disorders of the skin, mucous membranes, tongue, hair and nails, which result from malnutrition. The practical importance of these stigmata is that their presence should at once draw attention to the diet.

The dietetic principles underlying the treatment of malnutrition associated with neurological or psychiatric disorders are the same as these required for the treatment of malnutrition from any cause. The first essential is an accurate diagnosis of the nutritional deficiency. It should be remembered that dietary deficiency is seldom limited to one nutrient but is usually multiple. If possible, the deficiency should be remedied by a good mixed diet, supplemented if necessary by extra vitamins, minerals or protein. In severe cases, particularly in psychiatric disorders, special feeding methods may be required (Chapter 48).

Diseases of the central nervous system can be classified according to the following plan :—

1. Disorders of the cranial nerves.
2. The epilepsies.
3. Space-occupying lesions.
4. Cerebrovascular disorders.
5. Infections.
6. Demyelinating diseases.
7. Extrapyramidal syndromes.
8. Syringomyelia.
9. Motor neuron disease.
10. Disorders of peripheral nerves.
11. Deficiency diseases.

Disorders of the cranial nerves.—These may arise from many causes, but nutritional deficiency is rarely one of them ; nor does dietetic treatment usually influence their course. However, lesions of the second and eighth nerves are occasionally associated with nutritional disorders, as described in Chapter 33.

The epilepsies.—Epilepsy may be defined as a transitory disorder of cerebral function which recurs periodically in paroxysms and which is associated with a disturbance of consciousness and is commonly manifest as fits.

The epilepsies can be classified into two groups: (1) *idiopathic* or *constitutional*, of which the cause is unknown; (2) *symptomatic*, the cause of which may be (*a*) local disease such as a tumour, thrombosis or infarct, trauma, abscess, or a degenerative lesion of the brain, or (*b*) a generalised disease such as cerebral anoxia, a metabolic disturbance (uræmia, hypoglycæmia, severe hepatic failure) or poisoning (alcohol, lead, cardiazole). Neither idiopathic nor symptomatic epilepsy is due primarily to a nutritional deficiency.

Since the time of Hippocrates a great variety of diets have been used for the treatment of idiopathic epilepsy. Starvation is claimed to reduce the frequency of fits but has obvious limitations as a routine therapeutic measure. Other dietary restrictions advocated are reduction in the intake of sodium, of water and of foods rich in animal protein. Ketogenic and acid-producing diets have also been recommended. Proof of the value of such diets by controlled trials is conspicuously absent. For this reason and because they often impose unwarranted hardships on the patient, they cannot be recommended. Patients with epilepsy should take normal well-balanced meals at regular intervals but avoid large meals, which are known to predispose to fits, especially in children. The intelligent use of sedative drugs is of great value in treatment.

Some of the general causes of symptomatic epilepsy, *e.g.* uræmia, hypoglycæmia and hepatic failure, are amenable to dietetic treatment: these have been described in the appropriate sections of this book.

Space-occupying lesions.—Lesions within the skull, such as a tumour or an abscess, differ in their effects from those found elsewhere because they occur within a rigid cavity. Hence their development is commonly associated with an increase of pressure which has a detrimental effect on cerebral function. Such lesions differ in their ætiology in no way from similar lesions elsewhere in the body. The relationship of nutrition to infection is discussed in Chapter 56.

Cerebrovascular diseases.—Numerically this is the most important group of diseases of the central nervous system. More people die from strokes than from ischæmic heart disease, but the incidence of the latter has increased in recent times much more rapidly. The principal causes of cerebrovascular accidents are hypertension and degenerative vascular diseases, especially atherosclerosis. The ætiology of these disorders and the measures for their prevention and treatment have been discussed in Chapter 40. The conclusions reached are generally applicable to the prevention and treatment of similar lesions in the vessels of the central nervous system.

Infections.—Infections of the brain and spinal cord are particularly serious because of the likelihood of grave damage occurring to vitally important structures. Bacteria, spirochætes and viruses may be the causal agents. Syphilis was once a very important disease of the central nervous system, but neurosyphilis is now becoming rare. Likewise, the incidence of acute anterior poliomyelitis, which in recent years greatly increased, has fallen dramatically since the introduction of preventive vaccination. It is a striking fact that the children and adults of the well-to-do classes who have been well nourished are specially prone to develop this disease and in them severe paralysis and fatal results are apt to occur. Members of the well-to-do classes are brought up under good hygienic circumstances and hence are less likely to become immunised to minute doses of the virus transmitted in unclean food, water or milk, or by cross-infection.

Abscess of the brain has become much less common and most types of meningitis, a previously fatal disease, are amenable to antibiotics or chemotherapy. As already noted, there is no evidence that infections of the brain or spinal cord are due to deficiency of any food factor or that dietetic treatment influences the course of the infection.

Demyelinating diseases, extrapyramidal syndromes (Parkinsonism), syringomyelia and motor neuron disease.—The causes of most of these diseases are unknown. The demyelinating disease, disseminated sclerosis, is the most common in persons of European stock. There is no evidence that dietary measures are of any specific value in its treatment, nor in that of any other disease in this group.

Disorders of peripheral nerves.—The term ' polyneuropathy ' or ' polyneuritis ' indicates that many different peripheral nerves are affected, often symmetrically. The reader is referred to page 442 for a description of the nutritional polyneuropathies.

Polyneuropathy may also develop as a sequence to metabolic disorders (diabetes mellitus, porphyria), poisoning, especially with heavy metals (arsenic, lead, mercury), or certain infections (diphtheria, acute infectious polyneuritis believed to be due to a specific virus).

Dietetic treatment is only of value for the polyneuropathy due to nutritional disorders and to diabetes mellitus.

Deficiency diseases.—*Subacute combined degeneration of the cord.*—For information see page 448.

Wernicke's encephalopathy.—For information see page 446.

THE HÆMOPOIETIC SYSTEM

The anæmias may be classified as follows :—

I. **Anæmias due to deficiency of factors essential for normal blood formation.**

  A. *Iron.*
    1. Chronic nutritional hypochromic anæmia.
    2. Post-hæmorrhagic anæmia.

  B. *Cyanocobalamin (vitamin B_{12}) and pteroylglutamic acid (folic acid).*
    1. Addisonian pernicious anæmia.
    2. Nutritional megaloblastic anæmia of adults and infants.

3. Megaloblastic anæmia complicating pathological conditions of the gastrointestinal tract, *e.g.* extensive gastric resections, intestinal anastomoses, sprue, idiopathic steatorrhœa, and from infestation with the fish tapeworm *Diphyllobothrium latum*.
4. Megaloblastic anæmia of pregnancy.
5. Megaloblastic anæmia of liver disease.
6. Megaloblastic anæmia due to anticonvulsant drugs.

C. *Vitamin C.*

The anæmia of scurvy (p. 217).

D. *Vitamin B_6.*

The anæmia of pyridoxine deficiency (p. 247).

E. *Protein.*

The anæmia of protein deficiency (p. 461).

F. *Thyroxine.*

The anæmia of myxœdema.

II. **Anæmias due to excessive blood destruction (hæmolytic anæmias).**

1. Due to congenital abnormalities of the erythrocyte.
2. Due to circulating hæmolysins.
3. Due to infective, toxic or allergic factors.

III. **Anæmias due to aplasia or hypoplasia of the bone marrow.**

1. Idiopathic aplastic and hypoplastic anæmia.
2. Secondary aplastic and hypoplastic anæmia.

IV. **Anæmias of uncertain origin.**

Due to chronic infection, uræmia, rheumatoid arthritis, liver disease or widespread malignant disease.

V. **Other diseases affecting the bone marrow, spleen, liver and lymph nodes.**

IRON-DEFICIENCY ANÆMIAS

In considering the anæmias, it must never be forgotten that iron-deficiency anæmia constitutes by far the most important group of anæmias in all parts of the world, and is certainly the most common deficiency disease at the present time in all continents. Hundreds of such cases exist for every case of megaloblastic anæmia, hæmolytic anæmia or aplastic anæmia.

1. Chronic nutritional hypochromic anæmia

This is described in detail in Chapter 36 because it is considered to be a primary deficiency disorder. The reader is also referred to pages 173-183 for a discussion on the physiological aspects of iron metabolism.

2. Post-hæmorrhagic anæmia

A hypochromic microcytic anæmia is associated with any condition in which there is acute or chronic hæmorrhage. Bleeding may be from any site but occurs most commonly from a lesion in the alimentary tract. Piles and peptic ulcer are frequently responsible for this type of anæmia. Treatment of acute post-haemorrhagic anæmia consists of bed rest, the administration of sedatives and the correction of the peripheral circulatory failure by the transfusion of sufficient quantities of whole blood to restore the blood volume to normal. Thereafter iron should be given for at least a month. Treatment of chronic post-hæmorrhagic anæmia consists of measures to control the bleeding and the administration of iron and a good diet as described for chronic nutritional hypochromic anæmia on page 461.

Hookworm infection and anæmia.—Infection with hookworm is a common cause of anæmia in all tropical countries where there is ' wet ' cultivation of the land. The clinical and hæmatological features of the anæmia are similar to those of chronic nutritional hypochromic anæmia. A heavy infection with hookworms is always associated with anæmia. Smaller loads may be carried without ill-effect. Hæmorrhages occur at the site of the attachment of the worms to the intestinal mucous membrane. These are certainly in part responsible for the anæmia. It is possible that the worms may also in some way interfere with the absorption of iron.

Heavy hookworm infection seldom occurs except in populations whose dietary intake of iron is unsatisfactory. The hypochromic anæmia is then in part due to a poor diet and in part to the worms. This combination causes much ill-health ; it may reduce greatly the working capacity of both men and women and is thus directly responsible for the poverty of many families in the tropics.

Experience has shown that in treating anæmia due to hookworm, whether in a single patient or in a large community, satisfactory results can only be obtained by the use of a combination of vermifuges, dietary improvement and the administration of medicinal iron.

Heavy infection may cause severe anæmia with hæmoglobin levels below 4 g./100 ml. In such seriously ill patients, before administering a vermifuge, blood transfusions should be given and the general condition of the patient improved by bed rest, diet and medicinal iron. All vermifuges are potentially toxic and hence dangerous to patients who are markedly undernourished or anæmic.

THE MEGALOBLASTIC ANÆMIAS DUE TO A DEFICIENCY OF CYANOCOBALAMIN (VITAMIN B_{12}) AND PTEROYLGLUTAMIC ACID (FOLIC ACID)

Of the six different forms of megaloblastic anæmia classified in Group B (p. 649) only one (nutritional megaloblastic anæmia of adults and infants) can be said to be a primary nutritional disorder ; this disease is directly due to the ingestion of a diet deficient in folic acid. For further information see pages 469 to 472. The reader is also referred to the section on the anæmia preventing vitamins, vitamin B_{12} and folic acid on page 236.

Before discussing the ætiology and treatment of the other five types of megaloblastic anæmia, it is appropriate to consider their relative incidence in different countries. In Great Britain, and also in Europe and North America, Addisonian pernicious anæmia is by far the most important of the group. The next in importance is the megaloblastic anæmia of pregnancy and the puerperium, and the third is the megaloblastic anæmia complicating pathological conditions of the gastrointestinal tract. The nutritional megaloblastic anæmia of adults or infants, the megaloblastic anæmia due to liver disease and anticonvulsant drugs are seldom encountered even in large hæmatological centres such as the one in Edinburgh. Table 43, 2 shows the relative incidence of the different forms in 926 consecutive cases examined in Edinburgh. By contrast, in India, Asia and Africa, malnutrition and pregnancy are the two main factors concerned in the ætiology of the megaloblastic anæmias, while Addisonian pernicious anæmia is stated to be rare. This view may require to be modified in the light of a recent study (Metz *et al.*, 1962) of the concentration of vitamin B_{12} in the serum and the absorption of an oral dose of radioactive vitamin B_{12} in eighty-one Bantu patients with megaloblastic anæmia which showed that eighteen of these patients were suffering from Addisonian pernicious anæmia. Once again it seems desirable to emphasise that although the megaloblastic anæmias are a fascinating group of diseases exemplifying how modern scientific methods can elucidate and produce specific remedies for illnesses which only a few years ago frequently terminated fatally, nevertheless from the viewpoint of public health they are of minor importance compared with the vast number of cases of iron deficiency anæmia which causes so much chronic ill-health and economic inefficiency in every part of the world.

Megaloblastic blood formation develops when from any cause the supply of vitamin B_{12} or folic acid is not sufficient to meet the requirements for normal hæmatopoiesis.

The deficiency of vitamin B_{12} in Addisonian pernicious anæmia is due to the stomach gradually losing its power to secrete a factor (Castle's intrinsic factor) required for the normal absorption of the vitamin in the food. Defective absorption of vitamin B_{12} may also occur from a lack of intrinsic factor in patients who have had total gastric resections or very extensive gastric neoplasms. It is a very rare sequel to partial

TABLE 43, 2. *Ætiology of* 926 *cases of megaloblastic anæmia seen in Edinburgh between* 1940 *and* 1958

Addisonian pernicious anæmia			748
Non-Addisonian megaloblastic anæmia—			
(1) of pregnancy		101	
(2) of infancy		...	
(3) due to malabsorption syndromes		56	
sprue syndrome (cœliac disease, idiopathic steatorrhœa, tropical sprue)	32		
blind loop	7		
gastric operations	17		
(4) due to dietary deficiency		...	
(5) due to anticonvulsant drugs		5	
(6) due to hepatic disease		2	
(7) idiopathic		14	
			178
Total			926

gastrectomy, and, when it develops after this operation, it is probably due to the occurrence of a widespread gastritis which destroys the cells producing intrinsic factor. Another rare cause of vitamin B_{12} deficiency is its destruction, diversion or utilisation by bacteria multiplying in blind or stagnant loops of the small intestine and also its ingestion by the fish tapeworm (*Diphyllbothrium latum*), an infection which occurs chiefly in Finland. Lastly, resection or short-circuiting of the lower ileum, the site of absorption of vitamin B_{12}, will lead to the development of megaloblastic anæmia.

In all these conditions the parenteral injection of cyanocobalamin or hydroxocobalamin (p. 239) rapidly leads to normoblastic blood formation. When the megaloblastic anæmia is due to an abnormal intestinal flora in a blind or stagnant loop a suitable antibiotic should be given and correction of the anatomical defect, by surgical resection or anastomosis, should be performed if possible. Anthelmintics must be given for the expulsion of the fish tapeworms.

Intestinal malabsorption of folic acid from the jejunum is the main cause of the megaloblastic anæmia which occurs in the sprue syndrome (tropical sprue, idiopathic steatorrhœa and cœliac disease of children and adults). It is also the principal factor that is lacking in the megaloblastic anæmias of pregnancy, liver disease and following the use of anticonvulsant drugs as judged by the excellent effects produced by folic acid therapy. The result of administering cyanocobalamin in these conditions is usually unsatisfactory.

The ætiology of the megaloblastic anæmias in the last three groups is not fully understood. It is often stated that the megaloblastic anæmia of pregnancy is due to a combination of factors, namely dietary deficiency, malabsorption and increased demands. It is possible that endocrine changes occurring in pregnancy interfere in some way with the metabolism of folic acid.

General treatment.—Patients should usually be kept in bed until the hæmoglobin level is over 7 g./100 ml. (50 per cent.). No special diet is required for patients with Addisonian pernicious anæmia but the meals should be light and easily digestible. For information in regard to the dietetic measures for the correction of nutritional deficiency in the megaloblastic anæmia due to pathological conditions of the gastrointestinal tract and in nutritional megaloblastic anæmia, the reader is referred to pages 469 and 508. Blood transfusion will be needed for patients who are severely anæmic (Hb. less than 40 per cent.).

Special treatment.—Parenteral injection of cyanocobalamin should be given as soon as possible to patients suffering from Addisonian pernicious anæmia and the other forms of megaloblastic anæmias due to vitamin B_{12} deficiency, as discussed above. Maintenance treatment for life with cyanocobalamin will be required for all cases of Addisonian pernicious anæmia and megaloblastic anæmia due to gastric resection or gastric destruction by widespread malignant disease. For the recommended dosages see page 242.

Folic acid is the drug of choice for all other forms of megaloblastic anæmias. A dose of 10 mg. twice daily is usually adequate. Maintenance treatment with folic acid will not be required if the underlying causal condition can be corrected, which is usually possible.

THE HÆMOLYTIC ANÆMIAS (CONGENITAL OR ACQUIRED), THE APLASTIC ANÆMIAS (IDIOPATHIC OR SECONDARY) AND THE ANÆMIAS OF UNCERTAIN ORIGIN

Hæmolytic anæmias due to congenital abnormalities of the erythrocytes include congenital hæmolytic anæmia (acholuric jaundice) which is due to a defect in the formation of the red cells, and the hereditary hæmoglobinopathies in which the red cells contain one or more abnormal hæmoglobins. Other forms of hæmolytic anæmia are due to infections or toxic factors or to circulating hæmolysins. An example of the latter group is hæmolytic disease of the newborn in which the rhesus (Rh) factor is the sensitising agent.

FAVISM.—The hæmolytic disease, favism, which particularly affects people of Sicilian descent, is due to sensitivity to the ingestion of the broad bean (*Vicia faba*) or the inhalation of the pollen. This results in the general clinical features and hæmatological finding of an acute, severe hæmolytic anæmia with hæmoglobinuria. It has recently been demonstrated (*British Medical Journal*, 1961) that the red cells of persons who develop favism are deficient in the enzyme glucose-6-phosphate dehydrogenase. This enzyme defect, which is an inherited abnormality, is not infrequent in the inhabitants of many sub-tropical and tropical countries. As a result of this defect the red cells fail to keep their glutathione in the reduced state which seems to be necessary for maintaining their integrity. Sensitivity to a variety of drugs, including the antimalarial drugs, pamaquine and primaquine, with the production of a hæmolytic anæmia is now known to be frequently associated with the same defect. Since the cause of favism is a defect in enzyme production and not an abnormal immunological response to the protein of *Vicia faba*, it would seem incorrect to describe the disease as being due to allergy. In parenthesis, it should be noted that in malarious countries the disadvantages of a deficiency of glucose-6-phosphate dehydrogenase may be balanced to some extent by the protection it confers against malarial infection (Alison & Clyde, 1961).

MALARIA AND ANÆMIA.—The anæmia is a direct consequence of this disease and is a matter of great clinical and economic importance. The anæmia of an acute attack of malaria is due to the destruction of erythrocytes by the plasmodia which develop within the cells: hence it is usually classified as an acquired hæmolytic anæmia. It has been suggested that the anæmia may be partly due to a toxic inhibition of the bone marrow. A low level of reticulocytes and leucocytes in the blood during the active period of infection lends some support to this suggestion, as does the fact that the rate of the response of the anæmia to treatment varies greatly in different patients. The severity of the anæmia bears a close relationship to the intensity and the duration of the infection. Since the blood destruction is intravascular, most of the iron liberated from the destroyed red cells is retained in the body and hence can be used again for hæmoglobin synthesis. This explains how a patient's hæmoglobin level may return to normal following the cure of the malaria by chemotherapy without the administration of medicinal iron. If, however, attacks are frequent and severe, and especially if they occur in a person whose stores of iron are poor, *e.g.* because of long-continued malnutrition, or blood loss, a state of severe anæmia develops which will require for its treatment medicinal iron in addition to a well-balanced diet.

A vicious circle develops in patients suffering from chronic malaria—sickness, weakness and anæmia, economic inefficiency, poverty, malnutrition, bad housing and social conditions, reinfection. Experience has shown how effective malarial control can be in eradicating the disease from large areas and how remarkable are the benefits which ensue therefrom.

Primary (idiopathic) aplastic anæmia is a rare disease of unknown origin. Secondary hypoplastic and aplastic anæmia may be due to drugs used in medicine, chemicals used in industry, X-rays and radioactive substances or to long-continued wasting disease and infections. Since there is often no direct correlation between the dose of the toxic agent and the occurrence or the degree of marrow aplasia, it would appear that idiosyncrasy or hypersensitivity is of prime importance in the development of aplastic anæmia.

The pathogenesis of the anæmia which develops as a result of severe or long-continued chronic infection, renal failure, hepatic cirrhosis and malignant disease, is far from clear and results of treatment are often unsatisfactory.

In none of these anæmias is there any evidence to suggest that their cause lies in a deficiency of any nutrient.

Other Diseases affecting the Bone Marrow, Spleen, Liver and Lymph Nodes

Other conditions are usually described in textbooks of hæmatology, although they may or may not be accompanied by anæmia. They include such diseases as (*a*) acute and chronic leukæmia; (*b*) the reticuloses (lymphadenoma, lymphosarcoma, etc.); (*c*) multiple myeloma; (*d*) diseases of lipoid storage (Gaucher's disease, etc.); (*e*) polycythæmia vera; and (*f*) the hæmorrhagic diseases. This latter group contains such diverse conditions as hæmophilia, hypoprothrombinæmia, thrombocytopenic purpura and hereditary hæmorrhagic telangiectasis. Although the causation of many of these disorders is not known, there is no satisfactory evidence to suggest that nutritional deficiency is ætiologically important or dietetic treatment of any specific value.

CHAPTER 44

DISEASES DUE TO INBORN ERRORS OF METABOLISM

TO Sir Archibald Garrod belongs the credit of being the first physician to propound the idea that certain clinical disorders were due to inborn errors of metabolism, the result of alterations in chemical individuality. This conception was first published by him in 1902 and was illustrated by his studies of the rare disorder, alkaptonuria, which is recognised clinically by the excretion of urine which becomes black on standing. This is due to large quantities of homogentistic acid. This acid, a product of the breakdown of phenylalanine and tyrosine, is formed in the tissues of all persons but is normally rapidly broken down. In his Croonian Lectures, delivered in the Royal College of Physicians, London, Garrod (1908) described several other disorders which resulted from the consequences of chemical individuality such as pentosuria, porphyria and cystinuria, and suggested the title ' inborn errors of metabolism ' as a suitable name. His remarkable insight into this problem was also indicated by his observation that such inborn errors had a peculiar familial distribution, namely, that while two or more brothers or sisters in a family might have the stigmata of a particular error, the parents were not necessarily affected. In addition he noted that the parents were often close blood relations, either first or second cousins. On the basis of the above observations Garrod came to the conclusion that alkaptonuria and other inborn errors of metabolism were genetically determined and inherited as a recessive Mendelian character. Since the publication of Garrod's classic papers many such disorders have been described which conform to the genetical characteristics mentioned above, but which have very different chemical abnormalities and clinical features. One of the most interesting aspects of these disorders is the specificity of the metabolic defects. This is well illustrated in the condition, fructosuria, in which the patient is able to metabolise perfectly glucose and all other sugars with the exception of fructose.

The genetically determined mechanisms underlying each metabolic error is the absence of an enzyme required for a particular metabolic process. Thus, if the enzyme required for the conversion of phenylalanine to tyrosine is absent, phenylalanine accumulates in the blood and tissues. The excess is excreted in the urine, together with various derivatives of phenylalanine, in large amounts and the clinical disorder called phenylketonuria results.

While Garrod's conception of a metabolic block provides a satisfactory explanation of some disorders, in others, *e.g.* cystinuria, the essential error is a genetically determined defect in renal tubular function. It is of course possible that such a defect may be due to a failure in the production of an enzyme required for the active process of reabsorption. There are also various genetically determined conditions resulting from defects in protein synthesis. Examples of these are afibrinogenæmia and agammaglobulinæmia and the hæmoglobinopathies.

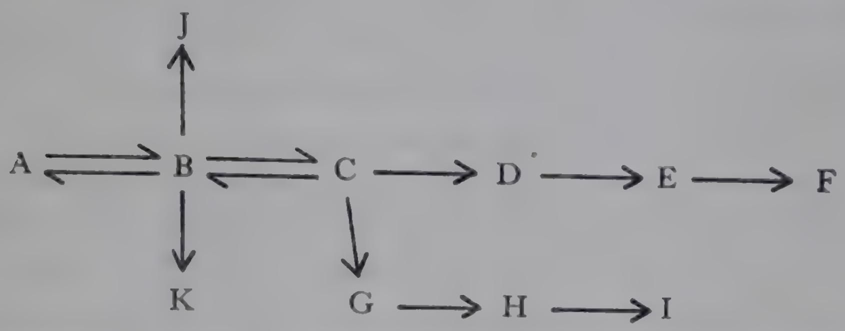
It is widely accepted that with the exception of uniovular twins, each individual is genetically endowed with his own particular chemical pattern, and that inborn errors may lead to a wide variety of disorders differing in their mechanisms of production and in their clinical effects. In some of these disorders, such as fructosuria and pentosuria, the patient's health is in no way impaired ; in others, such as phenylketonuria, there may be considerable morbidity but little mortality, while in galactosæmia fatal results frequently occur unless the appropriate dietetic treatment is instituted early in the disease. Chemical individuality is also well demonstrated by the existence in each individual of a specific blood group (A, B, AB, O) as originally classified by Landsteiner, and the more recent discovery of blood groups M, N and Rh systems.

A monograph by Harris (1959) deals concisely and lucidly with the many different varieties of inborn errors of metabolism and biochemical individuality. An excellent account of a Symposium on Nutrition and Metabolic Defects is given in the *Proceedings of the Nutrition Society* (1961). Harris classifies the inborn errors of *amino acid* metabolism into two groups. Group 1 includes the disorders which result from a metabolic block leading to a defect in intermediary metabolism due to a deficiency of a specific enzyme. Harris describes this group as the ' overflow amino acidurias ' because the mechanism of renal tubular absorption, although normal, is unable to deal with the greatly increased amounts of amino acids which pass into the urine. Examples are phenylketonuria, alkaptonuria and familial non-endemic goitrous cretinism.

Group 2 is called the ' renal amino acidurias ' because the primary defect is in the process of tubular reabsorption. In this group the plasma concentration of amino acids is normal and so is their concentration in the glomerular filtrate. Nevertheless excessive amounts are excreted in the urine because of insufficient tubular reabsorption. Group 2 includes (1) cystinuria in which the presenting feature may be calculus formation ; (2) the Fanconi group of syndromes where various amino acids are excreted in the urine, renal glycosuria is common, electrolyte disturbances occur and vitamin D resistant rickets in childhood may be an important feature ; (3) probably the ' maple syrup urine ' syndrome ; this rare condition is so named from the peculiar odour of the patient's urine and is totally unrelated to the New England delicacy. Affected infants usually die with severe neurological disturbances ; there are increased amounts of valine, leucine and isoleucine in the urine. The nature of the enzymic defect has not been discovered.

Harris includes in his group of inborn errors of *carbohydrate metabolism* the glycogen storage diseases, first described by Von Gierke in 1929, which result from a deficiency of glucose-6-phosphatase and other enzymes: galactosæmia; essential pentosuria; fructosuria; renal glycosuria and primaquine sensitivity. The last disorder results from a fall in the concentration of reduced glutathione in the red cells consequent on a deficiency of the enzyme, glucose-6-phosphate-dehydrogenase. This enzyme defect also causes sensitivity to various drugs and chemicals (particularly of the analine group) and is the cause of favism (p. 654).

The mechanisms whereby abnormal metabolism may arise from the defective production of an enzyme have been illustrated by Sinclair (1962) as follows:—



Block between C and D. If the enzyme that converts C into D is absent, at least four consequences may cause disease.

1. Lack of D, E, F. Examples are: (*a*) albinism, in which melanin cannot be formed from tyrosine; (*b*) familial goitre in which tri-iodothyronine cannot be formed; (*c*) hypoglycæmia in von Gierke's disease through lack of glucose-6-phosphatase.

2. Accumulation of C. Examples are: (*a*) homogentisic acid in alkaptonuria which by oxidative polymerisation stains urine, cartilage and other mesenchymal tissues; (*b*) L-xylulose in pentosuria, another of Garrod's inborn errors; (*c*) glycogen storage diseases caused by lack of liver glucose-6-phosphatase.

3. Accumulation of A or B. The high glycogen and high lactate of von Gierke's disease are examples.

4. Production of normally minor substances, G, H, I. Such metabolites, usually produced only in traces, occur in increased amounts in phenylketonuria and maple syrup urine disease.

Three further aspects must be mentioned before discussing in detail therapeutic measures. First, the intense scientific and clinical interest in the diseases due to inborn errors of metabolism is only equalled by their rarity. The disorders which occur most frequently are phenylketonuria and galactosæmia. In Edinburgh, in a population of approximately half a million and about 8500 live births annually, a most careful investigation has been carried out (Farquhar *et al.*, 1962) into the incidence of phenylketonuria, and the result shows that approximately one new case may be expected in every 2½ years. In the U.S.A., with a population of approximately 175 million persons, it has been calculated that phenylketonuria occurs once in every 20,000 births and that children with this syndrome account for about 1 per cent. of the patients in institutions for mental defectives, *i.e.* there are between six and nine thousand phenylketonuric mental defectives in the U.S.A. The rarity of such disorders as galactosæmia, cystinosis and the glycogen storage diseases is shown by the low incidence of such cases in the Sick Children's Hospital, Edinburgh, *i.e.* approximately 2 to 3 new cases of each disorder may be expected to be seen every 10 years (personal communication from Dr J. W. Farquhar). Other examples of inborn errors of metabolism are so rare that only a small number of cases are recorded in the total world literature.

Secondly, since these inborn disorders are genetically determined, it is not surprising that they are usually not influenced prophylactically by environmental factors including nutrition. This statement possibly requires some slight modification in the case of diabetes and gout, diseases in which a strong familial history can usually be obtained. Obesity, especially if due to excessive intake of fat, appears to increase the chances of an individual developing diabetes, provided he has in addition the inherent tendency to the disease. Likewise attacks of clinical gout are frequently related to overeating or to the eating of articles of food or drink to which the patient seems to have an idiosyncrasy.

Thirdly, genetically determined disorders and variations such as are related to altered structure of the hæmoglobins, of the plasma proteins and of the antigenic substances attached to red cells which determine the various blood groups, are not influenced by any treatment, including diet. Even in the case of those disorders due to inborn errors of metabolism of amino acids and carbohydrates, in only a few instances are the results of dietary treatment worth while. Two of these, namely phenylketonuria and galactosæmia, will be discussed at length.

PHENYLKETONURIA

Phenylketonuria is now known to be due to a genetic deficiency of the enzyme phenylalanine hydroxylase which is essential for the conversion of phenylalanine to tyrosine. In consequence the blood in particular and also the cerebrospinal fluid and urine of phenylketonurics contain amounts of phenylalanine and its pyruvate, lactate and acetate derivatives greatly in excess of normal. As a result of this accumulation, damage to the brain occurs which may be severe and irreversible unless treatment is instituted at an early stage. This has been clearly demonstrated in Knox's review (1960) of reported cases. Of the various clinical features which develop, mental deficiency, usually marked in degree, is the most important, but convulsions, tremor, rhythmic rocking of the body and posturing of the hands in front of the eyes also occur. Skin lesions such as dryness, roughness and eczema are common. In addition to these mental, neural and dermal changes, phenylketonuric children are often blond, fair-skinned and blue-eyed consequent on a defect in melanin metabolism.

Treatment

This consists of giving the infant or child a diet containing a very small amount of phenylalanine. Since phenylalanine is one of the *essential amino acids*, normal growth will not occur if it is entirely excluded from the diet. However, if the daily intake of an infant is reduced from the normal of about 100 mg./kg. body weight to approximately 15 to 25 mg./kg. body weight, the child will grow satisfactorily and the level of serum phenylalanine will fall to a normal or low normal value. Since this amino acid is present in all dietary proteins (2 g. of milk protein will contain about 100 mg.) there are great technical difficulties in providing sufficient protein to keep the patient in nitrogen balance and at the same time ensure a sufficient reduction in the intake of phenylalanine. In addition such a diet is expensive and difficult to prepare. Fortunately, commercial preparations are now available which provide the essential nutrients and yet keep the diet low in phenylalanine—Minafen (Trufood Ltd.) for infants; Lofenalac (Mead Johnson Ltd.); Cymogram (Allen & Hanburys Ltd.) for older children. Such preparations are made by processing casein hydrolysates so as to free them from phenylalanine and tryptophane and then adding to the product glucose, minerals and vitamins required for growth, energy and health. For further details of the dietary and biochemical control of phenylketonuria the reader is referred to the paper by Brimblecombe *et al.* (1961). Suitable sample diets and recipes are also available from the Hospital for Sick Children, London; an excellent account of the management of low phenylalanine diets has been produced by Mead Johnson Ltd. Patients can tolerate different amounts of phenylalanine in the diet and the tolerance may vary in the same patient at different ages. This amount can only be determined by frequent analyses of the phenylalanine concentration in the blood. For this reason and because of the difficulty in providing the child with a palatable diet low in phenylalanine it is essential that initially phenylketonurics should be treated in a hospital in which good biochemical and dietetic facilities are available, and by pædiatricians experienced in this particular field of medicine.

At the time of writing it is not possible to say how long the patient must adhere strictly to the diet. There is some evidence to suggest that it can be relaxed partially or completely when the patient has reached 13 to 15 years of age. The cost of the diet is very high. Apart from humane considerations, it is cheaper to treat these infants efficiently than to allow them to deteriorate into mental defectives with all the expense of institutional and nursing care which will be required for life.

There is good reason to believe that if efficient dietetic treatment is begun in time, *i.e.* within the first few weeks or months of life, the clinical features of this disorder can be prevented, or if already present, can be ameliorated. Unfortunately the results are far less satisfactory, especially in regard to the mental state, if treatment has been delayed beyond the first year. Mental retardation may be arrested but not reversed. In consequence much thought has been given to the problem of early diagnosis. This presents great difficulty as characteristic clinical features may not be recognised for six months after birth or even longer. Hence mass screening of all infants before they reach 6 weeks of age has been advised by some authorities. For this purpose the detection of increased amounts of phenylpyruvic acid in the urine by means of the 'Phenistix' paper strip test has been advocated. This is certainly a formidable task when it is remembered that the incidence of this disorder is about 1 in 25,000 infants. However, it is clearly indicated in the case of babies from phenylketonuric families and also in infants with mental deficiency, impaired growth, eczematous skin rashes, especially if the cause of these disorders is not apparent.

GALACTOSÆMIA

Galactosæmia is a well-established disorder due to a genetically determined inborn error of metabolism. There is a specific deficiency of an enzyme called galactose-1-phosphate uridyl transferase which is required for the conversion of galactose to glucose. The metabolic block occurs between galactose-1-phosphate and glucose-1-phosphate. A deficiency of this enzyme can be shown in the red blood cells and the liver of patients with this inborn error. Hence when patients with galactosæmia are given a test dose of galactose, the level of galactose in the blood rises steeply, to be followed later by the excretion of galactose in the urine. It is probable that the clinical and pathological features of galactosæmia are not due to the excess galactose in the body fluids, but to toxic effects resulting from intracellular accumulations of galactose-1-phosphate or one of its derivatives.

Clinical features

As is the case with other inborn errors of metabolism, the clinical picture varies in severity from case to case. In its most severe form the disorder may be manifest in infants within 2 or 3 weeks after birth, as indicated by vomiting, difficulty in feeding, loss of weight and the onset of jaundice. In such patients the spleen may be palpable and the liver greatly enlarged and very firm, and ascites may be present. Examination of the urine will show the presence of sugar (galactose) and also protein. Without immediate dietetic treatment of such severe cases death rapidly occurs. In mild to moderate cases the diagnosis may be missed because of the failure of the doctor to examine the urine of an infant who has infrequent vomiting and who is not thriving. If the disorder is allowed to continue for months cataracts are likely to develop and these may lead in time to blindness. Mental and physical retardation are also likely to occur.

Treatment

Successful treatment requires early diagnosis and the complete exclusion of lactose and galactose from the diet. If this is accomplished successfully and in time, the hepatic, mental, physical and ocular changes may be prevented. Even when pathological alterations have occurred in the liver, kidney and eye, these may be reversed or improved. In addition the proteinuria and galactosuria will disappear. Until recently the preparation of a galactose-free diet for infants presented great difficulty as this entails the rigid exclusion of milk, which is the main dietary source of galactose. Milk sugar (lactose) is a disaccharide composed of glucose and galactose. Many technical difficulties are encountered when an attempt is made to remove all the lactose from casein. Fortunately, there has recently become available commercially prepared synthetic milk powders in which lactose has been replaced by dextrin, dextrose and maltose (Galactomin—Trufood Ltd. ; Low Lactose Milk Food—Cow & Gate). For those infants with a hypersensitivity to even very small amounts of lactose in the diet, a malt and soya flour food (Wanderlac) manufactured by A. Wander Ltd. has been recommended. When suitably diluted with water this forms a vegetable milk equal in value to cow's milk. In addition to these lactose-free products, early mixed feeding with lactose-free food should be started. It is still not known whether children with galactosæmia must remain on a galactose-free diet for life or whether after a few years the diet can be modified.

CHAPTER 45

FEBRILE DISEASES

METABOLISM IN FEVER

FEBRILE diseases are marked by certain changes in metabolism, which must be taken into account when constructing suitable diets.

1. Increase in basal metabolism

For every degree Fahrenheit rise in temperature there is a 7 per cent. increase in the basal metabolism. As a result of the increased metabolism there is a greater combustion of nutrients which are derived from the body stores and tissues unless a very liberal diet is given.

2. Toxic destruction of body protein

Protein destruction in fever is excessive and may be two or three times as much as in health. Although hyperthermia itself causes some increase in the breakdown of body protein, the protein destruction in fever has little relation to the height of the fever and appears to depend on the severity of the infection.

In a long-continued fever, therefore, an effort must be made to prevent undue loss of body protein by the prescription of a diet in which the protein intake is in excess of the maintenance requirements in health. There is no ground for the old belief that a high protein intake will increase the height of the fever.

Apart from these theoretical considerations, the arrangement of the diet is made difficult by the anorexia which is present in most fevers, and which may be complicated by nausea and vomiting. Much can be done to combat the anorexia by ensuring that the mouth is kept clean. If the tongue is furred and sordes are allowed to accumulate, it is not surprising that the patient's distaste for food will be enhanced. The mouth should be washed or swabbed out with a weak solution of sodium bicarbonate or other mouth wash before and after every meal.

THE DIET IN FEVER

The introduction of antibiotics and chemotherapeutic agents has greatly reduced the length of most febrile illnesses. Formerly in diseases like enteric fever, pyrexia frequently persisted for 3 or 4 weeks, but now it is usually restricted to a few days as a result of treatment. In consequence the wasting and malnutrition that in the past were so frequently associated with long-continued fevers are fortunately rarely seen. Nevertheless there are still febrile illnesses in which the infection cannot be brought under control for a considerable time and in such cases the provision of an adequate diet is of great importance and often presents many difficulties. It is best to consider diet in fever under two headings: (1) fevers of short duration, *e.g.* pneumonia; (2) long-continued fevers, *e.g.* cases of enteric fever, tuberculosis and other specific infections not responding to antibiotics.

1. Short Febrile Illnesses

In fevers of short duration such as pneumonia, in which the result, favourable or otherwise, is a matter of days, not weeks, the diet should be constructed with the chief object of saving the patient from all possible exertion in the taking of his food; the actual amount of nourishment given is of less importance.

The diet should be an entirely fluid one, and should be given in the form of small feeds at frequent intervals, usually every 2 to 3 hours. Milk is the mainstay of the diet and about 2 pints (1 *l.*) should be given daily. This will provide about 40 g. protein and 700 Cal. If necessary, it may be citrated with 1 gr. of sodium citrate to 1 oz. of milk (0·2 g./100 ml.), and some of the milk feeds should be flavoured with cocoa, coffee or tea, or given as an egg switch. Two or three eggs may be given daily, switched in milk, or an egg and fruit drink. Liquid cooked cereals such as a gruel or any of the proprietary preparations, served with cream, and cup custards may be given at some of the feeds to vary the diet. Fresh fruit juice should be given in ample amounts for its vitamin content and also as a flavouring agent for the water, which should be supplied to the patient between feeds in liberal quantities.

One of the distressing complications of a severe febrile illness such as pneumonia is tympanites. Since the principal factor in its causation is a toxic paralysis of the bowel, correction of the toxæmia by appropriate means should be the basis of treatment, *e.g.* antibiotics or sulphonamides. In addition, measures for the relief of tympanitis may be of value. These include drugs such as pituitrin and carbachol, and dietetic restrictions. If the motions are loose and contain excessive amounts of curd, cream should be prohibited and milk reduced in quantity and citrated or diluted with water. The caloric intake may be maintained by fruit juices sweetened with glucose or lactose. On the other hand, if there is no evidence of impaired fat digestion and absorption, the tympanites should be treated by restriction of carbohydrate foods.

2. Long-continued Fever

If in 3 or 4 days a fever is not responding to antibiotics, it is necessary to take steps to see that the dietary intake, and particularly the intake of protein and calories, is sufficient to meet the extra requirements imposed by the fever. The principles governing the construction of the diet in these circumstances are :—

(*a*) The diet must have a high caloric value—up to 50 per cent. more than the normal maintenance intake. This means that the diet should yield about 2500 Cal./day.

(*b*) A liberal protein quota must be provided in an endeavour to make good the excessive destruction of body protein. Owing to the anorexia and the necessity for providing food in liquid or semi-solid form, it may not be possible to give more than 70 to 90 g. of protein daily, but this intake will usually cover the protein loss except in the most severe fevers.

(*c*) A large proportion of the food ingested should be in the form of carbohydrate. This will prevent ketosis, which may arise if the patient is burning his own body fat in increased amounts owing to the raised metabolism. The ‘ protein sparing ’ property of a high carbohydrate diet is also of practical importance.

(*d*) Food should be served in liquid or semi-solid form and must be easily digestible. Large meals should be avoided and the principle of small feeds every 2 or 3 hours adopted.

(*e*) Fluids must be given in abundance. Owing to the loss of fluid in sweat and the disinclination of patients to take fluids and food, dehydration may develop in fever. Fluids require to be given in greater amounts than are usually ingested, but excessive amounts must not be forced on the patient. A daily total fluid intake of about 5 to 6 pints (2½ to 3 *l.*) is ample.

Salt depletion occurs from sweating and this must be made good by adding sodium chloride to suitable feeds and to the glucose lemonade drinks. Diet No. 2 (p. 823) is a semi-fluid one, which may be used in the early stages of a long-continued fever. It contains approximately 2500 Cal.

As the patient improves and can take solid food, this diet should be modified progressively by the addition of toast or bread with butter or margarine, milk puddings, custards and stewed or fresh fruit, puréed vegetables, eggs and cream of chicken, rabbit and fish, and some of the feeds of the fluid diet can then be omitted. Formerly it was the practice to supplement the diet with vitamins. It is extremely doubtful if this is necessary provided the patient is taking an ample well-balanced diet as recommended above.

In convalescence the appetite is usually increased, but it is best to proceed slowly and not allow a food intake too great for the patient's power of digestion. The food should be easily digestible and rich in protein and vitamins. Foods such as pastries and cakes and highly seasoned and indigestible articles (p. 824) should be avoided. Diet No. 23 is suitable for use during convalescence.

CHAPTER 46

DIET AND ALLERGY

INTRODUCTION

THE word ' allergy ' means an altered or abnormal tissue reaction. Such a reaction may occur when there is contact between a foreign protein (an ' allergen ') and body tissues that are sensitive to it. The allergen may reach the tissues by direct contact with the skin or mucous membranes, or through the blood stream after absorption. A single allergen may cause reactions at several sites ; thus a patient allergic to egg protein may suffer a local reaction in the gut and also an attack of asthma when the absorbed allergen is carried by the blood to the lungs. Ingested proteins do not usually enter the blood stream unchanged, for they are normally split into their component polypeptides and amino acids in the gut ; these after absorption have no allergic properties. But sometimes small amounts of protein may be absorbed unchanged ; allergic manifestations may then occur.

The nature of an allergic reaction is not fully understood, but there is little doubt that it results from an abnormal effect of the combination of the antigenic allergen with antibody within the tissue cells. Cell damage apparently results, with the release of histamine which probably contributes to the clinical effects. Normal immune reactions between antigen and antibody evoke no such effects. The abnormality may lie in a congenital defect in the tissue concerned (since allergy is frequently inherited) or to previous slight exposure to the allergen in amounts insufficient to elicit an adequate antibody response and thus to confer immunity.

Allergic reactions have been classified into two types : (1) the ' immediate reaction ' type in which the allergic manifestations occur within 4 hours of the patient coming in contact with the allergen, and often within seconds or minutes ; in this form of allergy skin tests are nearly always positive ; (2) the ' delayed reaction ' type in which manifestations may not appear for many hours or even for 2 or 3 days ; in this type skin tests are usually negative. Once the allergic reaction has developed the resulting manifestations in the integumentary, gastro-intestinal, respiratory and nervous systems are the same in both types.

Allergic reactions may be trivial, *e.g.* a mild urticaria (nettle-rash), or may be so serious as to result in sudden death. Serious reactions are known as *anaphylactic shock*. The mechanism underlying this severe form is illustrated by the following experiment. A guinea-pig is made sensitive to the serum of another animal by a single small injection of the serum. This produces a specific antibody, but on an inadequate scale. Thereafter a second but larger dose of the serum is given, which results in profound and often fatal collapse of the animal. Anaphylaxis is most frequently encountered in people who receive a therapeutic or prophylactic injection containing some foreign protein to which they have been made sensitive by a previous injection of the same material.

Foods liable to give rise to allergic reactions

Food allergies are most common in infants and young children. Eggs, milk and wheat are frequently incriminated, presumably because they are the most important initial foods of the young. After the age of five there is a tendency to the spontaneous disappearance of food allergy, while allergy to inhaled substances such as pollens, dusts and animal hair and danders becomes increasingly frequent. The list of foods that have been claimed to cause allergic reactions is very large ; in addition to the foods mentioned above it includes such diverse items as fish (especially shellfish), various meats, nuts, mustard, tomatoes, celery, bananas and oranges.

A hypersensitivity to wheat protein (gluten) is certainly the cause of cœliac disease as discussed in Chapter 38, and a hypersensitivity to milk protein may be the cause of some cases of ulcerative colitis (Taylor & Truelove, 1961). These examples of hypersensitivity are claimed to be due to an allergic reaction because circulating antibodies to gluten and casein have been demonstrated more frequently and to a higher degree in cœliac disease and ulcerative colitis than in normal controls (Taylor *et al.*, 1961). It is possible, however, that these immunological responses develop secondarily to pre-existing gastrointestinal lesions which facilitate the entrance into the circulation of increased amounts of proteins such as gluten or casein respectively.

Clinical manifestations of allergy

Allergic reactions may affect any system of the body, producing one or more of the following manifestations :—

Skin : urticaria (nettle-rash or hives), angioneurotic œdema, eczema, purpura.
Respiratory system : ‘ hay fever,’ bronchial asthma.
Gastrointestinal system : dyspepsia, vomiting, abdominal pain, diarrhœa.
Cardiovascular system : circulatory collapse, shock and anaphylaxis.
Nervous system : headache.
Genito-urinary system : hæmaturia.
Locomotor system : swelling or hæmorrhages into joints (Schönlein's purpura).

Diagnosis

Whereas the diagnosis of the cause of the ‘ immediate reaction ’ type of allergy is often easy, the reverse is true of the ‘ delayed ’ type of reaction.

This may be extremely difficult because of the absence of positive skin tests and because the dietary history may be difficult to interpret and may in fact be misleading. Clinical features similar to those mentioned above may arise as a result of a great variety of organic diseases. Alimentary disturbances, such as dyspepsia, flatulence, biliousness, colic, vomiting or diarrhœa, believed to be due to allergy, may be caused by eating excessive amounts of indigestible foods, or by food poisoning. Such symptoms can also be caused simply by emotional disturbances, anxiety and worry. Psychological factors may intensify the liability to allergic reactions in sensitive patients. Allergic reactions themselves may be a cause of worry and distress and so may perpetuate a vicious cycle.

In view of these difficulties the following methods for the detection of food allergies are recommended.

Detection of food allergies.—DIETARY HISTORY.—A careful dietary history must always be taken. In some cases of food allergy the symptoms develop so rapidly and dramatically, almost immediately after eating the offending food, that the patient is able to make his own diagnosis. More often it is not so easy to associate symptoms with any particular food, especially if there is any considerable delay between the eating of the suspected food and the onset of illness. A particular food may be wrongly believed by the patient to be the cause of his allergy because it happened to be eaten immediately before an attack, which was in fact due to some other cause. In case of doubt, the patient should be given a diary in which he records with great care and detail over a period of many days or even weeks all the foods which he eats and the times of his meals. He should note in the diary any disturbances which he believes may be due to food allergy, recording the nature and intensity of the symptoms and the time of their occurrence. If a careful study of the diary suggests a relationship between the intake of a certain food and the onset of allergic manifestations the following tests should be carried out.

PROVOCATIVE FOOD TESTS.—The patient should be given a small quantity of the suspected food in a made-up dish, so that he is unaware that he is eating the food that he suspects and dreads. If the patient notes in his diary his typical symptoms at the appropriate interval after the meal, this strongly suggests that the food is responsible. Owing to the variability of allergic responses however, the test should be repeated two, or preferably three, times before either a positive or negative result is accepted. If a negative result is obtained on three occasions, it can be concluded that the symptoms are not due to the suspected food. If the tests are positive, then appropriate treatment must be undertaken as discussed on page 670. Provocative food tests should not be made in patients who develop severely allergic reactions immediately after the ingestion of a recognised article of food, not only because the test is unnecessary, but also because on occasions it can lead to dangerous anaphylactic shock.

STRICT ELIMINATION DIETS.—If the history, skin tests (see below) and trial and error with restricted diets fail to provide a clue to the diagnosis, strict elimination diets may be helpful. In the case of infants and young children this method is easier than in the case of adults, because of the limited variety of foods which they eat. It is possible to eliminate from a child's diet separately, and in turn, the common causes of children's food allergy : eggs, milk and wheat. In adults the procedure is much more difficult because of the extended range of foods to which sensitivity may develop. Hence various types of elimination diets have been devised with the object of discovering the offending article. Patients may have to be fed on such diets for many weeks before the offending article of food is discovered and, as the diets are complicated, they are normally only suitable for the investigation of patients in a hospital with a dietetic department and by a physician experienced in the subject of allergy. Diagnosis by the use of such elimination tests is tedious and time consuming for both patient and doctor ; it should be undertaken only when symptoms believed to be due to food sensitivity are seriously inconveniencing the patient. For further information the monograph by Rowe (1944) and the article by Fuchs and Strauss (1960) should be consulted.

SKIN TESTS.—These have been much used in the past. A minute quantity of an extract of the suspected food is injected into the skin or rubbed into a scratch. If a weal develops and there is a surrounding red flare, this is sometimes taken as indicative of sensitivity to the food in question. The presence of pseudopodia extending out from the weal may be taken as confirmatory evidence. Yet because a patient is sensitive to a foreign protein introduced into the skin in this way, it does not necessarily follow that he is sensitive to the same protein when taken by mouth. Moreover, the skin test may be negative to a protein which is producing allergic reactions elsewhere, *e.g.* in the gut. Such apparently contradictory results are not uncommon. A possible explanation is that the cells in contact with the allergen are not necessarily the site of production of the appropriate antibody to it. It is only when the allergen combines with its specific antibody that symptoms arise.

The value of skin tests is limited by the frequency of these false positive and negative results. If, however, there is a well-marked reaction to one single article of food, while tests of other food extracts are negative, this may be of real diagnostic value, especially if it confirms a suspicious history.

Treatment

ELIMINATION OF THE CAUSATIVE FOOD.—If a positive food factor is identified and can be eliminated from the diet, then the symptoms will not recur. For example, if the responsible article of food is one which is not consumed regularly (*e.g.* shellfish), it can easily be avoided : it is far more difficult in the case of eggs, milk and wheat, which are present in so many foods—cakes, puddings, sauces, gravies, soups, etc. Other methods must be tried in such a situation.

SUBSTITUTION OF ALTERNATIVE FOODS.—This is sometimes possible in the case of milk. A child sensitive to cow's milk may not necessarily be sensitive to goat's milk. There are proprietary preparations of soya bean which can be used as a substitute for milk. Similarly a child sensitive to wheat may do well on oats, rice or barley.

DENATURATION OF THE PROTEIN.—Sometimes if a protein is denatured by heat it ceases to act as an allergen. Thus a patient sensitive to raw milk or lightly boiled eggs may be able to take with impunity boiled milk or an egg which has been boiled for at least 10 minutes. Patients who are sensitive to eggs may be able to take the yolks, especially if well cooked, although the whites may continue to cause symptoms.

DESENSITISATION.—Many attempts have been made to desensitise patients who suffer from food allergy by repeatedly injecting small quantities of the allergen or giving small amounts by mouth. This method is generally regarded as being of little or no value in the case of food allergy and is not recommended.

EFFECT OF AGE.—In general, patients tend to outgrow their sensitivity to food allergens. Foods known to have caused reactions in childhood may be tried months or years later when it is found that they can be taken again with impunity.

DRUGS.—Adrenaline, ephedrine, aminophylline and corticosteroids are useful for the alleviation of the immediate symptoms of allergic reactions. The prescription of tranquillisers and sedatives is often indicated because of the close connection between emotion and allergy. Antihistamines are of value for preventing recurrences ; but no drug is capable of bringing about desensitisation.

GENERAL ADVICE.—It has already been said that every patient proved to be allergic to a particular food should be advised to avoid it, at least for a time. Some years later he may be allowed to try it cautiously, especially if it is an important article of diet. All people with a well-defined food allergy should know about it and inform their doctor ; otherwise they may suffer a severe or even fatal reaction from a therapeutic injection given for the treatment of some other disease. For instance, a patient sensitive to eggs may react badly to immunising injections prepared on an egg medium, such as those for poliomyelitis, influenza or yellow fever. Similarly patients who are sensitive to pork may develop an allergic response to soluble or zinc protamine insulin (prepared from the pancreas of pigs), should they develop diabetes mellitus and require insulin injections. Insulin zinc suspensions (as discussed on page 614) are useful in this respect since they are pure insulin, uncontaminated by species-specific protein adulterants. Injections of liver extract or adrenocorticotrophin (ACTH) derived from cattle may cause shock to patients who are allergic to beef.

MAINTAINING THE NUTRITION OF THE PATIENT.—Many intelligent allergic patients, knowing something of the nature of their disease, go to great lengths to avoid any food that may aggravate it. Some avoid so many kinds of food that they become severely undernourished. A similar result may follow from unwise advice from their doctors. This is particularly true in the case of growing children. It cannot be stressed too strongly that allergic patients should not be subjected to dietary restrictions without good evidence that their symptoms are due to an allergen in their food. In many cases this can only be determined in a clinic where the appropriate tests can be carried out.

CHAPTER 47

NUTRITION IN RELATION TO INJURY, SURGERY AND CONVALESCENCE

SEVERE injuries and many disorders requiring major surgical operations are frequently complicated by malnutrition. In the last 20 years an increasing number of surgeons have become interested in nutrition, a subject which now occupies an important place in surgical literature. The standard textbook on the subject is *Metabolic Care of the Surgical Patient* (Moore, 1959), a book which can be strongly recommended to all surgeons. There are also many other smaller books which give useful accounts of both the practical and theoretical aspects of surgical malnutrition. Among these is an excellent monograph by Wilkinson (1960).

Apart from primary malnutrition, directly attributable to an inadequate diet, a surgical patient can become malnourished in several ways.

Malnutrition secondary to surgical disease of the alimentary tract.—This can arise secondary to a variety of conditions which reduce appetite or interfere with swallowing or with digestion and absorption. Cancer of the œsophagus and the stomach are typical and common examples. Such diseases give rise to a cachexia which is indistinguishable from that of primary starvation as described in Chapter 26. There is a rapid wasting of adipose tissue, muscle and other lean tissues. Weight may decline rapidly and in extreme cases may fall by as much as 1 lb. (0·5 kg.) a day. In such patients the loss of nitrogen may be as much as 10 g./day, equivalent to 62 g. of protein. This will be associated with a loss of water of up to 200 g./day. There are also losses of potassium which may be as great as 30 mEq./day.

There is much experience to indicate that it is impossible either to prevent or to make good such losses as long as the surgical lesion persists. It is seldom justifiable to delay an operation whilst an attempt is made to improve the nutritional state of the patient. The immediate needs for protein can be met by giving adequate and repeated transfusions of plasma and whole blood. Then if the lesion is treated satisfactorily, the nutritional state of the patient will respond to the feeding methods discussed below.

The catabolic response to injury.—Any severe injury or major surgical operation leads to a generalised loss of tissue. Cuthbertson (1930) was the first to show that injury is followed by an increased excretion of urinary nitrogen due to a breakdown of proteins throughout the body and he has recently reviewed the effects of trauma (Cuthbertson, 1959). The resultant negative nitrogen balance is usually of the order of 12 to 15 g./day, corresponding to a loss of 350 to 450 g. of muscle and other lean tissues. This rate of loss persists for 2 to 3 days and then decreases, provided convalescence is proceeding satisfactorily. A negative nitrogen balance may, however, persist for as long as a week, even in cases in which the operation has been entirely satisfactory. Potassium loss from the cells also occurs and is often higher than the corresponding nitrogen losses. Healthy muscles contain about 3 mEq. of potassium/g. of nitrogen. During the catabolic phase after injury the K/N ratio in the urine may be as high as 7·5 mEq./g.

The cause of this tissue breakdown in response to injury or surgery is almost certainly due to an increased secretion of cortical hormones by the adrenal glands. This is part of the normal physiological response to stress and is mediated through the pituitary gland and increased secretion of ACTH. It is not possible to prevent this loss of tissue by dietary measures and, in so far as it seems to be a physiological response, there is little justification for attempting to do so. However, the loss must be made good when convalescence is established.

TABLE 47, 1. *Mean values for the loss of weight and other body substances by* 15 *patients after gastrectomy, and by* 4 *healthy controls during a period of* 4 *days. Both groups received no food for* 4 *days and no water for the first* 2 *days and limited water for the second* 2 *days* (*Modified from Wilkinson*, 1961)

	Patients after gastrectomy	Healthy controls
Weight loss (kg.)	4·13	3·26
Protein loss (N × 6·25 g.)	390	280
K loss (mEq.)	312	154
Na loss (mEq.)	167	264

(All values expressed per 65 kg. body weight)

A typical example of the loss of tissue that may occur after gastrectomy is given by Wilkinson (1961), whose data are reproduced in Table 47, 1. The losses of the patients are compared with those of healthy controls who underwent the same restrictions of food and water for a similar period of 4 days. During this period the patients' loss of weight was nearly 1 kg. more than that of the controls ; while the patients also lost 100 g. more protein and twice as much potassium. The figures in Table 47, 1 for the electrolyte losses in starving healthy persons, notably the large loss of sodium, suggest strongly that in simple starvation most of the water lost comes from the extracellular compartments. In contrast, when severe injuries or major surgical procedure cause malnutrition the source of most of the water lost appears to be the intracellular compartment.

Sepsis and malnutrition.—Malnutrition may develop in patients with chronic illnesses associated with sepsis. Large septic burns, infection of the site of a fracture, peritonitis or chronic abscesses in any part of the body are examples. The associated toxæmia may so impair appetite that little food may be eaten. Further, the accompanying fever, by raising the metabolic rate, will increase the needs for nutrients. Large negative balances of calories, proteins and other essential substances may result. Loss of weight may be rapid and can be as much as 1 kg./day. When a big area of skin is destroyed over a septic burn the direct loss of protein from the burnt surface may be very large, *i.e.* as much as 50 g./day.

The assessment of the nutritional state

In assessing the nutritional state of persons who have had severe injuries or undergone major surgical operations, the measurement of body weight is the most useful single test. Balances are now available which enable patients who are seriously ill to be weighed with a minimum of disturbance. These are being increasingly used in surgical clinics. The interpretation of changes in weight is, however, not always easy. Loss of tissues may be masked by the accumulation of œdema.

Protein deficiency.—This is undoubtedly the most important nutritional deficiency in surgical practice. The level of serum albumin is a useful index of the state of protein repletion. The lower limit of normality is 3·5 g./100 ml. The level in the serum is in part determined by the state of hydration. Thus dehydration leads to a reduction in plasma volume, and in consequence the level of albumin may be within normal limits, despite the fact that the total quantity of serum albumin may be greatly reduced. The use of the hæmatocrit and the measurement of the total blood volume may help in assessing these changes.

Electrolytes.—Disturbances of electrolyte balance, and most notably potassium deficiency, are frequent complications of surgical operations and severe injuries. These can be assessed by measurement of plasma levels of electrolytes and, if necessary, the rates of their daily losses in the urine.

Vitamins

Vitamin K is the vitamin of particular interest to the surgeon because, as discussed in Chapter 13, deficiency of this vitamin may be associated with a tendency to bleed consequent on hypoprothrombinæmia. Since vitamin K is fat soluble, a deficiency is likely to occur when a failure in fat absorption develops from any cause. In surgical practice this most frequently arises in diseases of the biliary system associated with jaundice (p. 209).

Vitamin C deficiency may develop in surgical patients. Operations, injuries and especially burns each cause an increased utilisation of ascorbic acid. This is probably part of the physiological response to stress and is brought about by induced activity of the adrenal cortex. The needs of such patients for vitamin C are therefore augmented. It has long been known that when there is severe depletion of vitamin C in the tissues, the healing of wounds may be grossly impaired (p. 217). In surgical practice in Great Britain and in other prosperous countries, frank scurvy is exceedingly rare, and it is very uncommon for depletion of reserves of the vitamin to be so severe as to prejudice the healing of wounds. The great majority of surgical patients do not require extra vitamin C in the form of synthetic ascorbic acid, provided they are given a well-balanced diet. However, in chronic illnesses, especially if sepsis is present, it is essential to make sure that the intake of the vitamin is adequate. In countries where the content of the vitamin in the usual diet is low, it is advisable to provide all patients, who have been severely injured or burnt or who have had major operations, with a good supply either in the form of fruit juice or as synthetic ascorbic acid.

DIETARY MANAGEMENT

Pre-operative.—As a surgical operation is a nutritional stress, it is desirable that the patient should be well nourished before undergoing this strain.

Weakness, loss of appetite due to anxiety and other causes, or gastro-intestinal atony or obstruction may create difficulties. In such cases special feeding methods as described in the next chapter may be needed. If the patient is able to eat normally, the special care of a dietitian is often invaluable. As Anne Sutherland (1955) has pointed out, routine hospital diets are often monotonous, and insufficient in calories and protein for rapid restoration of nutritional failure. Furthermore the nursing staff of a busy surgical ward have often insufficient time to devote to the special feeding of individual patients. The diet must be adjusted to the needs and tastes of the individual patient. If the patient is undernourished it is advisable to attempt to correct this situation provided the need for the operation is not urgent. Diet No. 10, which is high in calories and proteins, is suitable for this purpose. For those patients who are unable to take it, a semi-fluid diet, such as Diet No. 2, will be required. However, if the patient's malnutrition is directly attributable to a disease or an injury it is wrong to postpone the necessary treatment, whether surgical or medical, since it is very difficult, if not impossible, to achieve dietary rehabilitation until the surgical or medical condition has been corrected. While it is most unwise to starve a patient before operation, it is also dangerous to anæsthetise a subject whose stomach is full of food. This risk can be obviated by ensuring that the last meal before operation is light and is taken at least 3 hours before the anæsthesia is due to be given. If for any reason the start of the operation has to be postponed, the patient should be given small quantities of sweetened fruit juices in water at short intervals. This will help to maintain his reserves of calories and prevent dehydration.

Post-operative.—Neither fluid nor food should be given until the patient is fully recovered from the anæsthetic. Otherwise there is a risk that they will be inhaled into the lungs with the subsequent danger of aspiration pneumonia.

Gardner (1958) has shown that about 1 in 10 of surgical patients may inhale some food into their lungs, with consequent risk of pneumonia. The most common cause is trying to drink in recumbency. Cups designed to facilitate this should, he says, be abolished. Patients who cannot sit up to drink should drink through a straw. If this is not possible, special feeding methods (Chapter 48) must be employed. For many patients, feeding is best begun by giving frequent small feeds, each containing 25 g. of carbohydrate, as already recommended for use in recovery from diabetic ketosis (p. 621). If post-operative convalescence proceeds normally and there are no complications, the patient's appetite is usually a reliable guide to requirements ; there is no need to force food in the early stages of convalescence. If the post-operative patient is still seriously ill or there are surgical factors preventing a normal intake of food, then special feeding methods, as described in Chapter 48, will be necessary.

CONVALESCENCE

Proper feeding often has an important part to play in determining the speed with which a patient recovers from a surgical operation or serious illness, and hence to the length of time that he occupies an often much-needed hospital bed. The essential principles are to give ample amounts of protein in order to make good the drain on the body's reserves of protein caused by the catabolic phase and, if the patient is underweight, to build him up by providing plenty of calories. Routine hospital diets are often inadequate for these purposes. Furthermore, the patient's appetite may be fickle and the inclination to eat reduced by mental and physical fatigue. Every art of the dietitian may be needed to tempt his jaded appetite.

Once normal feeding has been re-established, a regime such as that set out in Diet No. 23 will be found satisfactory for most adult patients. Medicinal iron may be needed if the patient is still anæmic from previous bleeding.

There remains the problem of replacing the ascorbic acid lost in the body during the immediate reaction of trauma. Synthetic ascorbic acid tablets should seldom be necessary for this purpose. The vitamin is much better derived from natural sources—fresh fruit and vegetables—which provide many other useful nutrients besides.

Finally it should be remembered that many patients are necessarily confined to bed for long periods during convalescence—*e.g.* those recovering from multiple injuries involving fractures of bone, those requiring repeated skin grafts following extensive burns, or patients who have suffered from poliomyelitis or acute rheumatic fever. Prolonged immobilisation in bed often leads to extensive demineralisation of the bones. Physiotherapy and occupational therapy can do much to check this process by keeping the movable parts of the body active ; at the same time a high calcium intake, provided by plenty of milk, is desirable, to assist remineralisation. The calcium lost from the bones is excreted in the urine and, if the flow of urine is sluggish, calcium stones may develop in the urinary tract. A high fluid intake (2 to 3 *l.* daily) should be encouraged, to ensure that the urine is sufficiently dilute to keep calcium salts in solution.

OBESITY, SURGERY AND INJURY

Obesity predisposes to a variety of maladies such as hernia, varicose veins and gall-stones, for which operation may be required. Obese patients are also poor anæsthetic risks. If the need for an operation on an obese patient is not urgent, it may be wise to postpone it until some reduction in weight has been achieved by dietetic treatment (p. 389). This may help the surgeon and anæsthetist in their immediate technical tasks and perhaps improve the patient's ability to recover more quickly. The management of obese patients who are also diabetics and who require an operation, is described on page 628. As has been pointed out in Chapter 2, obese persons are more liable to accidents and injuries in the street, the home and the factory than persons of normal weight. Hence the importance of preventing obesity from developing.

CHAPTER 48

SPECIAL FEEDING METHODS

PATIENTS are often unable to take by mouth sufficient quantities of ordinary foods and fluids to supply their daily needs or to make good previous deficiencies. The circumstances under which this may arise are many and include :—

1. Any severe illness such as a continued fever, prolonged sepsis, extensive burns or malignant disease : these may result in loss of appetite and leave the patient too weak to take sufficient food to meet his increased requirements. As already described in Chapter 26, some victims of famine are reduced to this condition.

2. Cancer or any other disease of the mouth, pharynx and œsophagus, which obstructs the passage of food and so makes normal feeding difficult, if not impossible (Chapter 38).

3. Patients who are unconscious or delirious and so unable to feed themselves, *e.g.* with hepatic failure, in diabetic coma, acute uræmia or with a severe disease or injury of the brain.

4. Peptic ulcer with severe spasm and pain not responding to oral treatment.

The supply of calories and protein and of fluid and electrolytes presents special problems which must be considered separately.

CALORIES AND PROTEINS

Four methods are available for giving extra calories and protein : (1) normal foods taken by mouth may be enriched by adding suitable supplements ; (2) food may be introduced into the stomach by a tube passed through the nose or mouth down the œsophagus—intragastric tube feeding (gavage) ; (3) food may be introduced into the stomach or jejunum through a tube inserted at an operation for gastrostomy or jejunostomy ; (4) nutrients may be given parenterally.

It was the practice in days gone by to give foods of various kinds per rectum. Nutrient enemas have now been abandoned, because only very small amounts of nutrients were absorbed and rectal irritation was frequently produced. A solution of glucose is still occasionally given per rectum when, for some reason, an intravenous infusion cannot be administered. For the purpose of supplying calories this procedure is of limited value because not more than about a quarter of the daily requirements can be absorbed by this route.

Oral supplements

Increased intakes of calories and protein can be obtained by enriching ordinary foods such as milk, proprietary milk preparations, soups, soufflés, jellies, cakes and ice-creams with casein, fat emulsions or sugars. Proprietary preparations of casein and of fat are on the market. They can be incorporated readily into other foods and this is facilitated by the use of a mechanical blender. ‘Complan,’ ‘Casilan’ and ‘Prosparol’ are three which we can recommend from personal experience. Complan (Glaxo Ltd.) is a powdered preparation of milk proteins: 100 g. provides 31 g. of proteins, 44 g. of carbohydrate and 16 g. of fat, and it is also rich in minerals and vitamins, though low in sodium. Casilan (Glaxo Ltd.) is a preparation of milk proteins, almost devoid of fat, carbohydrate and sodium. Prosparol (Duncan Flockhart, Edinburgh) is a fat emulsion containing 50 per cent. of a vegetable oil: in 100 ml. there are 45 g. of fat with a caloric value of 405. Lonalac (Mead Johnson) is another milk protein preparation almost devoid of sodium.

TABLE 48, 1. *Ingredients for an oral supplement to an ordinary diet, sufficient for one meal*

Component	Amount	Protein	Fat	Carbohydrate	Calories
	g. or ml.	g.	g.	g.	
Complan . . .	125	39	20	55	550
Prosparol . . .	50	...	23	...	200
Sugar	20	...	...	20	80
TOTAL .	...	39	43	75	830

These preparations can be mixed together in any proportion and a number of recipes made up. Table 48, 1 gives the ingredients for an 800 Calorie meal rich in protein. A variety of flavouring agents—coffee, vanilla, strawberry, etc.—may be added. If cane sugar or glucose is used, this will make any mixture very sweet; hence many patients prefer lactose as a source of carbohydrate. The components can be made up with varying quantities of water to different consistencies and served either as a hot drink or a cold ice-cream. If a little gelatin is added, the whole mixture can be made to set as a jelly.

With suitable encouragement it may be possible to persuade patients to take sufficient quantities of such concentrated foods to enable satisfactory progress to be made during convalescence from severe medical illnesses or from operations.

Intragastric tube feeding (gavage)

Technique.—It was formerly the practice to pass a wide-bore stomach tube through the mouth into the stomach. The nutrients were poured into a funnel attached to the tube, and thereafter the tube was removed. The procedure was repeated three or four times in the 24 hours. Far more satisfactory results are obtained if a thin soft tube is passed into the stomach via the nose. Rubber Ryle's tubes have been now replaced by plastic tubes. Tubes with an internal bore of 3 to 4 mm. are suitable. If a partial obstruction is present in the œsophagus, a fine tube must be employed and its passage is facilitated by weighting its end with 5 ml. of mercury in a rubber bag.

Patients find the soft nasal tubes comfortable. The distance from the nostril to the stomach varies from 22 to 26 in. in different individuals. The tube should be lubricated with olive oil or liquid paraffin. While usually unnecessary, in nervous patients the nose may be sprayed with a solution of procaine. It will generally be found that one nostril is more patent than the other, and this side should be used for the initial passage of a tube. When about 8 in. of the tube have been inserted it will have reached the pharynx, and the patient will tend to cough or retch. At this point he should be encouraged to swallow, with the result that the tube will enter the œsophagus: thereafter it can be pushed quickly down into the stomach with little or no discomfort to the patient. Little difficulty will be found in patients who co-operate and who retain the swallowing reflex. When this reflex is lost, or when a patient is in coma, or delirium, the tube may have to be directed manually behind the epiglottis into the entrance of the œsophagus. The insertion of a thin wire stylet inside the tube may facilitate its passage. It is absolutely essential in all cases to be sure that the tube has passed into the œsophagus and not into the trachea, since the introduction of fluid into the lungs causes intense discomfort to the patient, and may even lead to a fatal result. If the tube is in the trachea or bronchus, dyspnœa and coughing occur immediately, and air can be felt and heard issuing from the outlet of the tube.

The most important point to remember is that fluid should never be introduced into the tube unless a sample of gastric juice has first been aspirated. Having made certain that the tube is in the stomach, it is strapped to the forehead and connected with a gravity drip apparatus, fixed in position to a stand about 2 ft. above the level of the patient. The rate of flow is controlled by a screw clamp. Delirious and insane patients may attempt to pull the tube from the nose, and this must be prevented by adequate sedation and, if necessary, by splinting the arms. Although we have left a tube in position in the same nostril for six days without any apparent harm, we recommend that the tube should be withdrawn every 48 hours, washed and boiled, and reinserted into the stomach through the other nostril. Once in position, the patient complains of little or no discomfort, and no interference with sleep usually results. Another advantage of the transnasal route is that it leaves the mouth unobstructed so that the patient can cough and spit in comfort, and can supplement the gastric feeds by oral ingestion if he is able and wishes to do so.

ADVANTAGES.—Gastric feeding through a tube has many advantages over parenteral feeding (p. 684) when adequate food cannot be taken by mouth.

1. All types of nutrients in adequate amounts can be supplied.

2. Foods and medicines which may be distasteful to the patient can be given without any distress.

3. Large quantities of fluid can be given daily by the gastric tube with safety. This is a matter of great importance in dangerously dehydrated patients.

4. The dangers of parenteral feeding (venous thrombosis, pulmonary œdema and cardiac dilatation) are avoided.

5. Intragastric tube feeding may be continued for weeks on end without danger or real discomfort to the patient if the transnasal route is used. In contrast intravenous infusion of glucose and amino acids presents many technical difficulties if it has to be carried on for more than a few days.

6. If it is desired at any time to empty the stomach, its contents can be aspirated through the tube, and this can be followed by gastric lavage if deemed necessary.

CONTRAINDICATIONS.—Gavage is contraindicated in patients who have recently undergone operations on the stomach. It is obviously impracticable if there is an obstruction to the passage of the tube in any situation between the mouth and the stomach, or in the presence of pyloric stenosis or high intestinal obstruction.

INDICATIONS.—Even with skilful oral supplementation it is difficult to give a very debilitated patient more than about 2250 Calories daily. With this intake the positive energy balance will only be small and in a week the most that can be anticipated is a gain in weight of about 1 lb. (0·5 kg.). This is quite inadequate for the treatment of emaciated patients when substantial gains in weight are required. For these the aim should be an intake of at least 3000 Calories with 100 g. of protein daily for 7 to 14 days and a gain in weight of about 3 lb. (1·5 kg.) in a week. These figures for anticipated changes in body weight assume that there is no marked change in body fluids. If there is dehydration, which is simultaneously corrected, gains will be much greater: conversely loss of œdema fluid will mask a weight gain due to a simultaneous laying down of tissue.

Table 48, 2 gives a formula for an intragastric tube feed (Dudley, 1958). A day's food providing 3700 Calories is made up in 2500 ml. of water. The feed can be given either by a continuous drip, day and night, or in five 4-hourly feeds. Fig. 48, 1 is an example of a satisfactory result with this method, used both before and after operation in a patient with a cancer of the œsophagus. If this patient's daily energy expenditure is taken as 1700 Cal., the excess intake over the 48 days was about 55,000 Cal. The total nitrogen retention was about 400 g., equivalent to about 2·5 kg. of protein with a caloric value of about 10,000. Thus about 45,000 Cal. were stored as fat (*i.e.* about 5 kg. of fat were laid down).

TABLE 48, 2. *A mixture suitable for intragastric feeding providing a daily ration of 3700 Calories*

Component	Amount	Protein	Fat	Carbo-hydrate
	g. or ml.	g.	g.	g.
Complan (Glaxo) . .	200	62	32	88
Prosparol (Duncan Flockhart)	400	...	180	...
Evaporated milk . .	400	30	34	37
Glucose	100	...	...	100
Hepovite (Evans) . .	60	30	...	29
Water to	2500	...	...	...
TOTAL .	...	122	246	254

300 mg. of ascorbic acid are added daily. Hepovite is a liver preparation rich in proteins and the B group of vitamins.

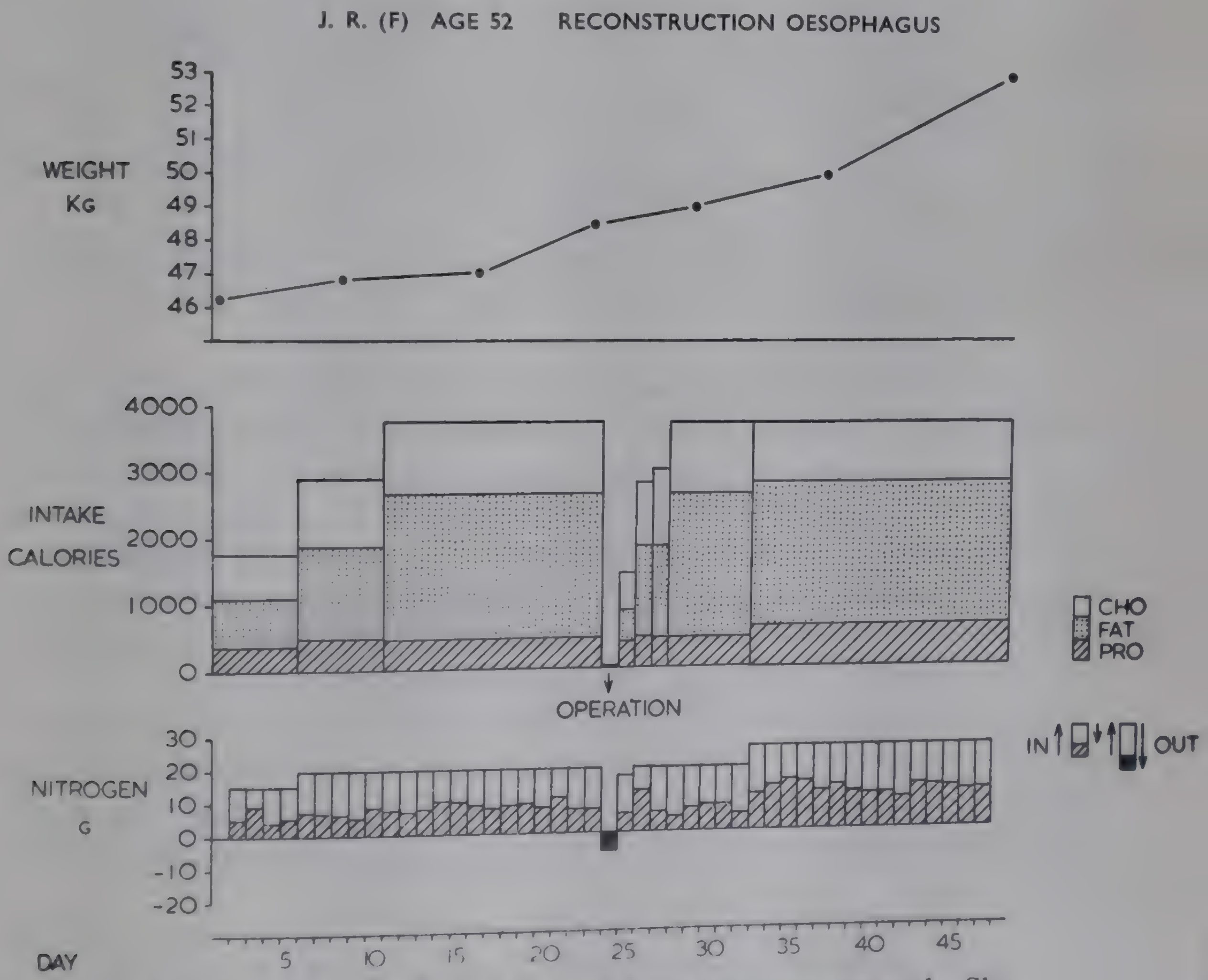


FIG. 48, 1. A woman, aged 52, had an œsophageal neoplasm removed. She was grossly undernourished when admitted, but gained weight steadily with nasogastric tube feeding. Note the cessation of intake on the day of operation and the steady gain in weight in spite of surgery. Mr A. B. Wallace's patient. From Dudley (1958).

The gain in weight by the patient over the period was 7 kg.—a little less than the calculated gain of protein and fat. This may be explained by the patient being in slight negative water balance.

Cases of peptic ulcer not responding to oral treatment usually respond rapidly to the intragastric milk drip. During 24 hours 6 pints (3 *l.*) of citrated milk is dripped into the stomach at the rate of about 30 drops per minute. A supplement of ascorbic acid is added to the milk.

The gastric secretion of hydrochloric acid is completely neutralised, and symptoms are rapidly relieved, while nutrition is maintained. When pain has been absent for 3 or 4 days the milk drop should be given between 8 P.M. and 8 A.M. and oral feeding (Diet No. 2) between 8 A.M. and 8 P.M. In a few more days intragastric tube feeding can be discontinued.

Intravenous feeding

Technique.—The fluid may be passed into the vein either through a needle or a cannula. If superficial veins in the limbs are prominent, it is simple to insert a needle. If, however, the veins are so collapsed or lie so deep that they are not accessible, a suitable vein must be exposed under local anæsthesia ; a cannula is then inserted and tied in. Both the insertion of a needle and the tying in of a cannula are simple procedures, which should cause little or no discomfort to the patient and be free from local complications. However, to achieve these results it is essential to pay close attention to technical details. An excellent account is given by Dudley (1961). Equipment for intravenous fluid therapy of children is described by Farquhar *et al.* (1961).

Although it is possible to administer all the essential nutrients by intravenous infusion, this presents many difficulties and it is seldom practical to give a complete day's diet by this means.

PROTEIN can be provided either by a protein hydrolysate or by a mixture of amino acids. Amino acids are expensive and protein hydrolysates liable to give rise to febrile reactions. Plasma proteins can also be used as a source of nitrogen and it is possible to supply the total needs of patients for nitrogen by intravenous infusion of concentrated plasma proteins. Much of the nitrogen given intravenously may be lost in the urine and so not available for tissue synthesis : it may also be used as a source of energy unless ample carbohydrate is given simultaneously.

FAT EMULSIONS suitable for intravenous injection are available, but they are expensive. Hitherto most preparations were liable to give rise to reactions and had a short ' shelf life.' Improved preparations are becoming available and these are likely to be more extensively used in the future.

GLUCOSE is usually given into superficial veins in concentrations of 5 per cent., because higher concentrations are liable to cause thrombosis of the veins. Two litres of a 5 per cent. solution will provide only 100 g. of glucose and a little less than 400 Cal. If glucose in large quantities has to be given, as may be necessary in the treatment of acute hepatic failure (p. 538), a 10 per cent. or stronger solution must be administered through a polyethylene tube inserted into a large vein.

ETHYL ALCOHOL can also be administered intravenously. Provided the amount given does not exceed 8 g. (10 ml.) per hour, intoxication will not arise. Wilkinson (1960) has recommended giving as much as 192 g. (240 ml.) in a 6 per cent. solution over 24 hours. This will provide 1300 Cal. If 10 ml. of absolute alcohol is added to a bottle of intravenous fluid, this will provide useful calories and also act as a mild sedative.

Intravenous feeding has a place in surgical practice, particularly when there is grave disease of the digestive tract, such as an obstruction or paralytic ileus. It may also be life-saving for some medical patients with acute uræmia, hepatic or diabetic coma. It is possible to meet minimum requirements for nutrients and at least prevent deterioration for several weeks by intravenous feeding. But it is a method to be used only under exceptional circumstances. The dangers are very real. McNair and Dudley (1959) report 11 cases in which either a staphylococcal septicæmia or a thrombosis of a large vein occurred in patients being fed by caval catheters. Of these 9 died, the catheter being the cause of death certainly in four and probably in four others.

Both at Belsen concentration camp and in the Bengal famine probably more lives were lost than saved by the use of intravenous feeding. A limited supervisory staff was unable to deal with the many technical difficulties and the severe reactions that occurred. It is doubtful, even at the present time, whether parenteral feeding methods should be used under famine conditions. Geyer (1960) has written an excellent review of what can and what cannot be acheived by intravenous feeding.

Subcutaneous infusions

As absorption is slow and so only limited amounts of fluid can be given, this route is now seldom used except when no suitable vein is available. It is most likely to be required for infants and young children. Isotonic solutions of glucose or saline may be run in through a needle inserted under the skin, usually on the front of the thigh or the outer side of the chest over the pectoralis major muscles. Infusions at two sites may be given simultaneously.

Intraperitoneal infusions

These were formerly given, but absorption from the peritoneal cavity is slow and this route has been largely abandoned. If it is used, great care is necessary to avoid sepsis.

Rectal infusions

Water, saline or glucose saline can be absorbed from the rectum. The maximum rate at which fluid can be absorbed by this route is about 150 ml./hour. This will be sufficient to meet normal physiological requirements, but not to make good the losses that may have occurred in a dehydrated patient.

If adequate quantities of fluid are to be absorbed, close attention to the details of technique is required, especially the avoidance of distension of the rectum. Before beginning to give the fluid, the lower bowel must be emptied and washed out with saline. This must be repeated each day before the period of infusion. The apparatus consists of a nozzle of glass or vulcanite, with a wide bore, attached to a glass Y tube, one arm of which is connected by thick rubber tubing to the drip apparatus: the other arm is connected with a piece of rubber tubing which acts as a free limb for the escape of flatus. The tubing near the nozzle is secured to the thigh by a bandage, while the fluid reservoir is attached to a stand about 12 in. (30 cm.) about the level of the rectum. The rate of flow must not cause rectal distension. It should start at twenty drops per minute and may be gradually increased to about forty drops per minute. The patient is likely to be most comfortable and the fluid best retained if he lies on his left side with his buttocks raised on a pillow.

Gastrostomy and jejunostomy feeding

Feeds can be given through tubes inserted at operation into the stomach or jejunum. Feeding by either route will often enable weight to be maintained, but lost tissue is seldom replaced. A mixture similar to that recommended for intragastric tube feeding can be used. Resort to gastrostomy and jejunostomy feeding is necessary only when it is impossible to pass an intragastric tube or, in the case of jejunostomy, when there is gross disease of the stomach.

WATER AND ELECTROLYTES

Deficiencies of water and electrolytes are most easily corrected by the oral route including intragastric tube feeding, but this may be difficult or impossible under the circumstances already listed at the beginning of this chapter and then parenteral replacement is essential. Intravenous infusion is the method of choice. Only in this way is it possible to be certain that absorption is rapid and complete. Fluid may also be given subcutaneously, intraperitoneally or per rectum. These routes should only be used when for some technical reason intravenous infusion cannot be given. They are now seldom used.

It is beyond the scope of this book to deal fully with the many problems presented by fluid replacement therapy. There are several excellent monographs on the subject, notably that by Wilkinson (1960). Here only a brief outline of some general principles is given. Parenteral therapy may be used either for replacement of losses that have already taken place or for maintenance when an oral intake is impossible. When the intake by mouth ceases or is insufficient, water continues to be lost in the urine and insensible excretion from the lungs and skin. Some electrolytes will also be lost but the main deficiency is of water. A frequent cause of deficiency of both water and sodium is loss of gastrointestinal secretions from diarrhœa or vomiting. States of potassium deficiency may develop under similar circumstances and whenever there is marked wasting of tissues.

When parenteral therapy, and particularly that by the intravenous route, is used certain elementary rules and precautions should be observed. The decision on what solution should be used and how much should be given must be based principally upon a careful history of the nature and duration of the fluid and electrolyte loss and upon an evaluation of the amount needed for maintenance purposes. Rapid changes in weight may occur as a consequence of either loss or administration of fluid, and weighing the patient daily is a useful means of both assessment and control. A careful record of fluid intake and of output should be kept for all patients who receive parenteral fluids, and this balance chart should include a space in which can be written instructions on the quantities of fluid and electrolytes which are to be given.

It should be remembered also that parenteral therapy has potential hazards both local and general. Any solution can irritate the wall of the vein and glucose is particularly prone to do so ; the aseptic phlebitis produced is not dangerous, unless bacterial invasion of the clot occurs ; then septicæmia may result. This is particularly liable to happen if a polyethylene catheter is passed into one of the great veins, as may be required, for example, in the treatment of hepatic failure or in diabetic coma : therefore such a technique should not be used without due regard to the potential hazards.

Amongst general hazards, that of overloading the body with fluids has been most emphasised. Two types of such overloading may occur : on the one hand an excess of water with sodium retention produces œdema which is manifest initially as crepitations at the lung bases, but which will become generalised unless the intravenous infusion is temporarily stopped ; on the other hand overloading with water alone may result from the giving of parenteral fluids in excess of the body's ability to excrete them, as may happen in the early period after surgical operations when urinary output is often reduced. This overloading is not associated with any characteristic clinical signs of retention of excess fluid ; it must be recognised from the marked gain in body weight, from the careful scrutiny of the fluid balance chart and from the general symptoms of apathy, lethargy, coma and convulsions that may be produced.

Parenteral administration of water and glucose

Water without electrolytes is usually required for maintenance purposes or to correct unrecognised insensible losses of fluid from the skin and lungs. For this purpose glucose is the best non-ionic substance with which to make an infusion fluid isotonic with the blood. A concentration of 5 to 6 per cent. (280 to 320 mM.) is recommended, as this produces a solution which is both isotonic and relatively non-irritant to the vein.

Parenteral administration of water and sodium

This is required when the extracellular fluid is reduced, usually as a result of the loss of sodium and water in approximately the proportions that they occur in the body. This produces the clinical picture described as dehydration in which the skin is dry and inelastic, the eyes sunken, the tongue often but not always dry and the peripheral circulation either actually or potentially inadequate. Isotonic sodium chloride (Solution 1, Table 48, 3) is the principal fluid required for replacement. When clinical evidence of dehydration is present a total volume of about 4 *l.* will be required to replace the deficit in extracellular fluid. In urgent situations most of this can advantageously be given within a few hours ; if the pulse is weak and the blood pressure low, the first litre of saline may be replaced by a litre of plasma or plasma substitute in order to expand selectively the reduced and inadequate plasma volume.

Occasionally, it may appear that a greater deficit of sodium than water is present. For example, in heat exhaustion (p. 811) large quantities of sodium and water are lost in the sweat, but the patient may have replaced only the latter by drinking water alone. In salt-losing nephritis (p. 586) sodium deficiency may result from the uncontrolled renal losses. Such deficits which are accompanied by low levels of sodium in the serum can be made good by the intravenous infusion of small quantities of 5 per cent. saline solution (Solution 2, Table 48, 3). Hypertonic saline should be used only under careful clinical and biochemical control. The calculation of the amount to be given can be made approximately from the serum sodium concentration if it is assumed that the extracellular volume is normal : for example, if the serum sodium is 120 mEq./*l.* before treatment is begun and it is desired to raise it to 140 mEq./*l.* in an extracellular volume of 12 *l.*, the total sodium required will be $20 \times 12 = 240$ mEq. This will be provided by 280 ml. of 5 per cent. saline.

For maintenance purposes in patients who have a continued extrarenal loss of sodium the amount to be given depends on the nature and volume of the loss. Any desired amount of sodium and fluid can be given by suitable combinations of solutions of isotonic sodium chloride and isotonic dextrose.

Treatment of a disturbed acid-base balance

In diabetic coma acidosis is frequently associated with a deficiency in the volume of extracellular fluid. This is also the case in alkalosis which occurs in severe vomiting. Potassium loss may be associated with both these conditions, although in acidosis serum levels of this ion are usually high while in alkalosis they are often low. If the dehydration is treated with isotonic saline, the kidneys, provided they are healthy, can usually correct the disturbance of the acid-base balance by the secretion of the appropriate alkaline or acid urine. In acidosis they can be assisted in this task, if the sodium ion is given in association with an organic ion, which can be disposed of by oxidation in the tissues : this leaves an excess of sodium ion to be excreted by the kidneys. Sodium lactate is suitable for this purpose and Solution No. 3 (Table 48, 3) is widely used in the treatment of acidosis.

TABLE 48, 3. *Composition of solutions used for electrolyte replacement* (Modified from Wilkinson)

Number	Solution	Constituents	g./100 ml.	Concentration of Components (mEq./*l.*)					
				Na	NH_4	K	Cl	HCO_3	Lactate
...	Extracellular fluid .	...	...	140	...	5	103	25	1
1	Isotonic saline . .	NaCl	0·9	153	...	...	153	...	...
2	Hypertonic saline .	NaCl	5·0	855	...	...	855	...	...
3	Saline lactate $\left(\frac{M}{6}\right)$.	Na lactate	1·8	161	...	...	...	...	161
4	Sodium ammonium and potassium chlorides	NaCl NH_4Cl KCl	0·35 0·35 0·13	63	... 70 ...	 17	63 70 17	... ...	... ...

Correction of potassium deficiencies

The concentration of potassium in the extracellular fluid is low and severe toxic manifestations with cardiac irregularity and arrest occur if the level is more than slightly increased. The administration of potassium by the intravenous route carries therefore a real hazard. However, it must be borne in mind that the amount of potassium administered parenterally is usually small in comparison with total body potassium with which the additional ions are rapidly equilibrated : provided renal excretory function for potassium is normal, excesses are rapidly eliminated by this route. Thus the need for caution should not lead to the administration of homœopathic amounts in the doubtful expectation of correcting a large deficit. When clinical signs of potassium loss are present, or when the serum potassium is low, or when the history suggests that a long-continued uncompensated loss of potassium has been taking place, the net reduction in total body potassium is rarely less than 300 to 400 mEq. and may be in excess of 1000 mEq. (total body potassium is between 3500 and 4000 mEq., see p. 142). In starving patients, losses of this magnitude may make a significant contribution to the mental apathy and gastro-intestinal atony which is a factor in the failure to secure an adequate oral intake of food.

With this knowledge in mind it is possible to plan the intravenous administration of potassium on rational lines. Between 100 and 150 mEq. daily can be safely given as part of a continuous infusion, and if the total fluid volume administered is 2½ *l.* this implies a potassium concentration of between 40 and 60 mEq./*l*., which is quite safe provided the rate of intravenous infusion does not exceed 200 ml./hr. The replacement of the body's needs for potassium is best achieved by adding concentrated potassium solutions to the day's intravenous fluids. This is easily achieved by having available a supply of ampoules of potassium chloride which contain 1 g. (13 mEq.) in 2 ml. of water. One ampoule can be added to one bottle of 5 per cent. glucose or normal saline. One litre of this solution (52 mEq.) can be given intravenously during a period of about four hours. If the plasma potassium remains low, an additional litre of fluid containing 4 g. of potassium chloride (52 mEq.) can be given.

For correcting electrolyte losses associated with excessive vomiting, Solution No. 4 (Table 48, 3), a mixture of sodium, ammonium and potassium chlorides, is often useful. This fluid can be infused with safety if the rate does not exceed 500 ml./hour. The total volume which should be given must also be judged by assessments of the fluid lost.

PART V—PUBLIC HEALTH

CHAPTER 49

THE ÆTIOLOGY OF NUTRITIONAL DISORDERS

IN presenting an account of the subject of nutrition and nutritional disorders to students of medicine and dietetics, it is necessary to include for consideration a range of subjects far more extensive than is usual in textbooks of medicine. The reason for this is not far to seek. It is now accepted that good health depends on an adequate food supply and this in turn on a sound agricultural policy and a good system of food distribution. The social, economic and agricultural factors that determine the food supply also determine the state of health and the incidence of disease amongst a population. These are the basic ætiological factors causing nutritional disease and, since neither rational treatment nor prophylaxis is possible without an understanding of causes, they must be subjects for study.

Throughout the world the total agricultural production is barely keeping pace with the total growth of population. Political and economic barriers impede the distribution of what food is available, but it is reasonable to hope that man may so conduct his affairs that the shortages and restrictions, with which almost every country in the world was afflicted after the end of hostilities in 1945, may not return. Only a blind optimist could think that the road to plenty and free choice is easy, or likely to be traversed quickly. In many countries medical students at present at universities will be struggling throughout their professional lives to maintain the health of their patients against a background of food shortages. The importance of this background in determining general levels of health and reactions to disease will vary from country to country and from society to society. In addition to the actual treatment of disease, the medical profession should help to shape public opinion so that people demand sensible nutritional programmes—both national and international. The doctor, who is respected by all sections of the people either as a man of magic or science, has an important role to play as an educator. Only by the wide propagation of a sound knowledge of basic health principles is it possible to create the demand for proper health policies. For these reasons it is imperative that the medical and dietetic professions should be familiar with the broad outlines of the social, economic and agricultural factors which determine food supply.

A further difficulty that arises is the diversity of nutritional problems in different parts of the world. Although the scientific principles of nutrition are universally applicable, an account of these principles would remain abstract and academic if practical problems were not considered. For instance, the methods for rationing milk in Great Britain were at one time a matter vital to our general health, but can only be of academic interest in Calcutta. Similarly the alleviation of famine following a failure of the monsoon is of urgent importance in parts of the tropics, while it is of no practical interest to a doctor in New Zealand. It is hoped that this chapter will interest those concerned with the fundamental factors which lead to underfeeding and malnutrition in different parts of the world.

CAUSES OF UNDERFEEDING AND MALNUTRITION

The fundamental causes of both underfeeding and malnutrition either of individuals or communities can be ascribed either to an insufficient supply of suitable foods or unequal distribution of the supply available. The manner in which these causes operate will now be sketched in broad outline.

Insufficient food production

The fundamental dependence of a satisfactory food supply upon a flourishing and sound agriculture is self-evident. It is a fact which has been realised from the earliest times, and has formed the basis of policy for innumerable wise rulers and leaders of mankind throughout history. Nevertheless the importance of a sound agricultural economy was generally overlooked throughout the 150 years before the First World War. During this period the energies of the ablest of mankind had been mainly involved in exploiting the incredible riches provided by the industrial revolution. Throughout the Americas, Africa, Asia and Oceania an apparently inexhaustible supply of land, fresh to agriculture, became available for producing the foods necessary for the industrial populations. Although much underfeeding and malnutrition was present in the poorer sections both of industrial and agricultural communities throughout the world, the wealth and prosperity of the successful or privileged minority at the top prevented all but a few of the clear-sighted from realising the extent and severity of underfeeding among the masses at the bottom of the economic scale. The world wars, with their interference first with food distribution and then with food production, gradually awakened the people of most countries to the importance of the relationships between food, agriculture and population.

Agricultural development is keeping pace with the growth of population in some countries but falling behind in others. Table 49, 1 shows some estimates for food supply in relation to population in various countries of the world. It will be seen that in Western Europe food supplies have returned to their pre-war level and in North America and Oceania they remain high. In Latin America, the Far East, Africa and the Near East

Table 49, 1. *Trends of average per caput calorie supply in selected countries*

Country	Average per caput calorie supply			
	Pre-war	1948-50	1951-53	1959-60
	Per caput per day			
Western Europe :				
Austria	2930	2670	2700	2950
Denmark	3420	3240	3340	3340
Finland	2990	2980	3070	3120
France	2870	2800	2840	2940
Germany, Western	3040	2730	2870	2890
Greece	2600	2490	2460	2900
Ireland	3400	3430	3500	3570
Italy	2510	2310	2480	2710
Netherlands	2840	2930	2900	2970
Norway	3210	3100	3100	2980
Switzerland	3140	3170	3120	2980
United Kingdom	3110	3130	3110	3290
North America :				
Canada	3010	3110	3050	3150
United States	3150	3180	3150	3130
Latin America :				
Argentina	2730	3240	2980	3040
Brazil	2150	2360	2410	2500
Chile	2240	2370	2430	2450
Uruguay	2380	2920	2950	3110
Venezuela	...	...	2010	2300
Far East :				
India	*1970	1640	1740	2080
Japan	2180	1900	1960	2210
Pakistan	...	2030	2000	1930
Philippines	1910	...	1940	2010
Africa and Near East :				
Egypt	2450	2370	2410	†2650
Israel	...	...	2780	2810
Turkey	2450	2510	2730	2850
South Africa	2300	2640	2690	2580
Oceania :				
Australia	3300	3220	3170	3330
New Zealand	3260	3360	3350	3430

Data from FAO, (1957, 1961).

* Includes Pakistan.
† United Arab Republic, Egyptian Region, 1957-58.

the supplies per head are slightly higher than 25 years previously, although for most countries in these regions they remain far below any estimate of national needs.

That underfeeding is associated with much ill-health is well known. That agricultural surpluses are associated with overfeeding and consequent widespread degenerative disease is only just being appreciated. It is only too apparent that the present methods of international trade have failed to solve the economic problem of how to distribute the surpluses of American, Canadian and Australian products to hungry people in many lands. Fig. 49, 1 shows the dilemma which still confronts mankind.

In India and China, where about half the population of the world exist, immense increases in agricultural production are necessary if widespread underfeeding and malnutrition are to be eliminated. No escape is left from the conclusion that only a fundamental revolution of agricultural methods can alter their present state of chronic semi-starvation, punctuated by episodes of acute famine.

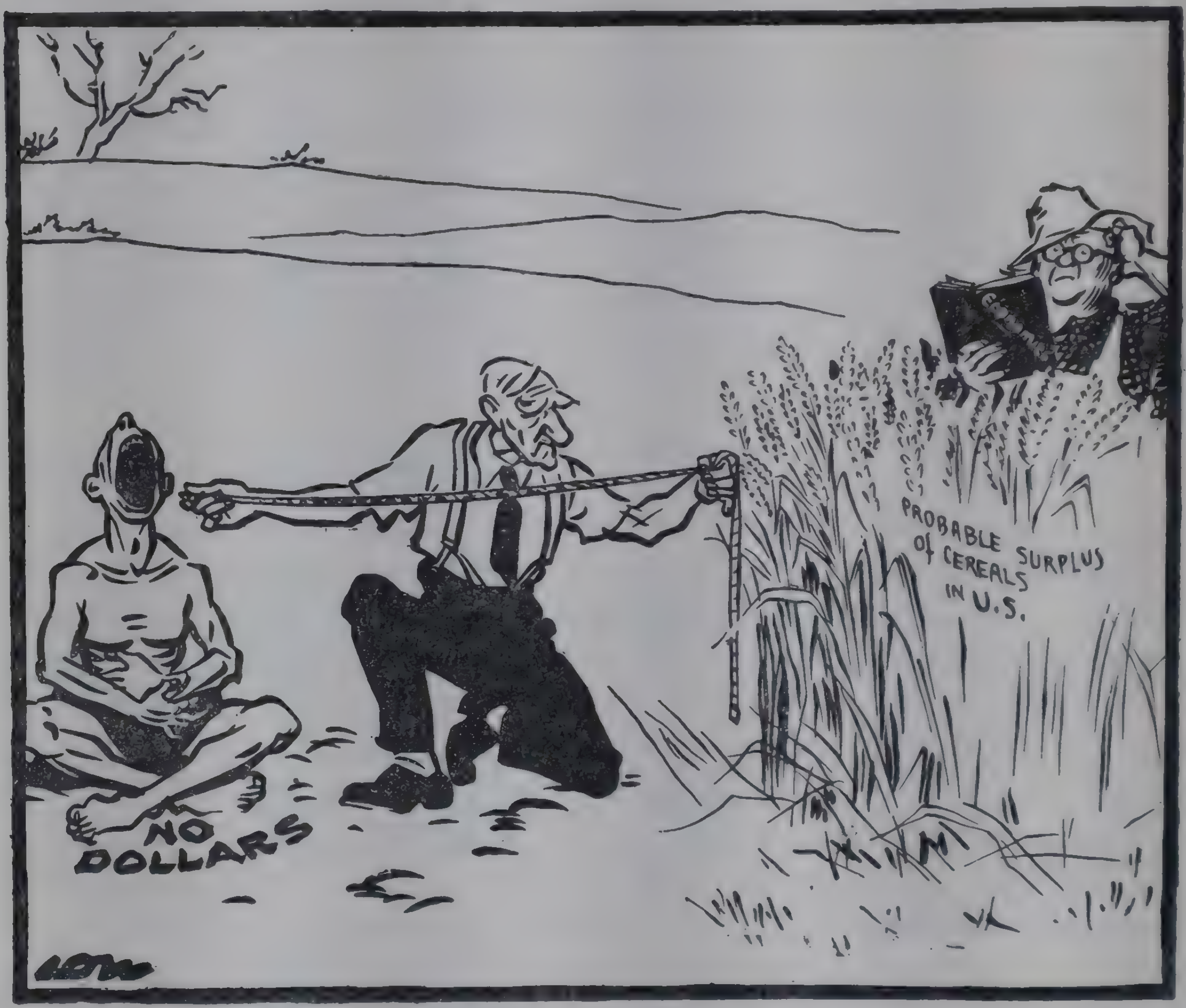

PROBABLE SURPLUS OF CEREALS IN U.S.
NO DOLLARS
LOW

Fig. 49, 1. ‘From land to mouth.’ Lord Boyd Orr, first Director-General of FAO. (With acknowledgments to the *Evening Standard*, 26th August 1946.)

The chief causes of agricultural unproductiveness may be discussed briefly under four heads :—

Climatic irregularities and catastrophes.
Soil erosion.
War.
Inefficient farming.

Climatic irregularities.—It is a curious anomaly of nature that in Great Britain, where the daily variations in the weather are so marked and unpredictable as to colour general conversation and social planning, the seasonal variations from year to year are small. British farmers may have good or bad harvests according to the season, but their 'bad years' bear no relationship to the catastrophes which regularly afflict farmers in the large continents as a result of variations in rainfall. In parts of Africa, the Americas, Australia, India and China there are areas many hundreds of miles in extent subject to periodic failure of the annual rain supply. In years of failure the total rainfall may be less than 20 per cent. of the average seasonal supply. Such years may alternate with years of floods when mammoth continental rivers, swollen by excessive rain in the mountains from which they spring, burst their banks and so destroy the crops. Water engineers play a most important part in determining the health of the people. The husbanding of water in dams and artificial lakes, its controlled distribution through irrigation canals and the management and control of huge rivers in flood are technical problems, the satisfactory solution of which is intimately bound up with nutrition, world health and civilisation.

At the primitive level, irrigation depends upon the village well, often worked by age-old devices like the Persian Wheel (Plate XXII). At the other extreme there are the huge river dams as on the Nile, gigantic projects involving the capital expenditure of many millions of pounds which bring fertility to great tracts of desert and improve the nutrition of hundreds of thousands of people. At the beginning of the first Five Year Plan in India in 1950, the irrigated area was 52 million acres. In 1960 the figure was 70 million acres, which is expected to increase to 90 million acres by the end of the Third Plan in 1965. A modern feature is the link-up between irrigation and the production of hydro-electric power. Plans of similar magnitude have been developed for harnessing the great rivers of America, Australia and Africa. It is upon the continued success of these schemes that the ever-increasing population of the world must rely for future food and health.

Soil erosion.—The next most important problem in food production is the prevention of soil erosion and the recovery of land previously degraded by bad agriculture. The immediate agencies of erosion are wind and water, following removal or damage to the pre-existing plant cover. The cause of this damage is usually the improper exploitation of the land in grazing, ploughing, firing, felling or the collection of domestic fuel. This improper or too violent exploitation itself results from pressures—financial or biological.

A common sequence of events in many districts now barren has been as follows. Originally forest existed. Men came, exploited the forest wealth too rapidly and cut down too many trees. Small areas of arable land were interspersed with acres of waste, broken by large tree stumps. At this stage or earlier, goats were introduced. These beasts are the antithesis of good animal husbandry. Goats differ from cattle and sheep in their ability to grub up the roots of plants and consume them. Goats also eat the leaves and bark of trees and so kill them. Thus the soil was loosened and in succeeding rains washed away, leaving an arid desert or a barren hillside. One of the most striking examples of this process is to be seen in the deserts of North Africa. Few of the millions of soldiers of many nations, when striving to exist and to survive during the last world war in that barren and hostile land, can have pictured the country as it was in the glory of the Roman Empire, rich and fertile—a main source of grain and olive oil to metropolitan Rome. After the collapse of the Roman Empire, ' instead of a numerous peasant population who understood the land and tilled it industriously, nomads wandered through the desert with their flocks of goats, sheep and camels. It is not that the climate had changed, though it may have done a little, but in destroying the Roman Empire in North Africa the Berber and Arab tribes nearly destroyed the land itself. The dams and reservoirs in which the Romans had hoarded the precious water were broken or filled with sand. As a result the winter rains poured down the wadis and into the sea, taking with them much of the fertile top soil. And by recklessly grazing their flocks the nomads destroyed the natural forest and vegetation so that the sun and wind and rain stripped the earth from the hills. With nothing to stop it the desert, which can move like an army, slowly crept down to the coast. In many parts of North Africa this process is still going on to-day ' (Pringle, 1947).

Similarly, in a region that is now part of Iraq and Iran, huge irrigation schemes, fed by the Tigris, Euphrates and Karun, once supported a large and vigorous population whose civilised arts of writing and sculpture record the earliest history of mankind. To-day the proud city of Cyrus and Darius is a mound of earth in the middle of a desert, over which nomads graze their starveling flocks. The last of the dykes on which its agriculture depended was finally destroyed by Timur (Tamerlane) in the fifteenth century.

There are few countries in the world where land degradation in one form or another is not of major importance for the health of future generations. South Africa, Australia, Pakistan, India and many British colonial territories are all afflicted. Vigorous counter-measures have begun in the U.S.A., the country of pioneers both in land spoilage and in eventual costly cures.

War.—War has always been a potent cause of nutritional diseases. It acts by interfering with food distribution, by taking away many of the young men from their normal task of agriculture, and sometimes by the destruction of crops and livestock on a large scale. In the past, civil wars have wrought the most havoc in this respect. The Thirty Years War in Europe, the Maharatta Wars in India, the wars that set up the Communist regime in Russia and the civil wars in China have all led to disruption of agriculture and so to famine on the grand scale. The Second World War was accompanied and followed by almost universal food restrictions amongst victors and vanquished alike. It should now be abundantly clear that these are the inevitable concomitants of all wars. This was not adequately appreciated before 1939.

Inefficient farming.—Ideally, farmers throughout the world should have enough basic education and capital to profit from the enormous developments of scientific knowledge. As yet the majority of the world's farmers possess neither of these essentials to reap the benefits of such knowledge. Applied science has as much to teach agriculture as it has already taught industry.

The great majority of the peoples of the world exist in undeveloped agricultural countries. Here they take part in a struggle for existence under conditions that have changed but little for thousands of years. More than half of the world's people still face the elemental problem of getting enough to eat. Those readers who have not had opportunities for travel can get a good picture of farming conditions at present existing in large parts of the world from a study of the Old Testament. In many countries conditions have changed but little from the time of the Pharaohs. Cairo is a fine modern city ; yet within a few miles of the Mohamet Ali Mosque there are villages in which one can see all the simple features of primitive agriculture, which are familiar to the reader of the Bible : the threshing floor, the oxen ploughing, the old men, the asses, the camels—all remain unchanged. A similar picture can be painted in many parts of the world—India, China, the East and West Indies, South America and Southern Europe, and an even more primitive one, without wheel or plough, in most countries of tropical Africa. The great increase in the inhabitants of the world necessitates new and better methods of food production.

Even in relatively well-developed countries the conditions are far from satisfactory. There can be little doubt that even the great efforts made to improve agriculture in Great Britain under the stimulus of war fell far short of its real potential which has not been reached at the present time.

Unequal distribution of food

As a cause of underfeeding and malnutrition, the unequal distribution of food within a society is second only in importance to insufficient production. *Poverty is by far the most important factor* responsible for this unequal distribution ; it affects urban communities, particularly in the enlarging towns of developing countries, more severely than those living in rural areas who have the opportunity to produce all, or a part, of the food they require. The relation between food, health and income in Great Britain in 1935 was studied by Boyd Orr (1936). His survey covered 1152 families, in each of which the total food consumption was weighed for one week and a correlation made between food consumption per head and available income per head in each family. It was found that those in the lowest economic group, which was believed to comprise 4½ million people (10 per cent. of the total population), were living on diets which failed to reach proper standards in almost every respect, especially in calories, proteins, vitamins A and C, and the minerals, iron and calcium. In the next two economic groups, containing 40 per cent. of the population, although the calorie and protein intake was satisfactory, intakes of vitamins and minerals were below standard. No serious student of nutrition has contradicted Orr's principal conclusion that between 1930 and 1935, 10 per cent. of the population of Great Britain had insufficient money to purchase sufficient food for themselves : these people were underfed.

It is important to remember that at this time the overall food supply of Great Britain was satisfactory. Estimates agree that the total available food, as retailed in the shops, was equivalent to 3000 Cal./head/day. This is more than was available in the country throughout the period of the Second World War and the immediate post-war period and was ample for the people if it had been properly distributed.

The fact that, despite ample national food supplies, the system of distribution was so unsound that one in ten of the people were underfed, is a major indictment of the economic structure of our society between the two world wars. Only when the imagination has grasped the full implications of this failure upon individual families and homes is it possible to appreciate the new quality of British society. During the long period of food shortages, which occurred during and after the Second World War, successive Ministers of Food regulated by means of rationing, subsidies and controls, the distribution of food according to human needs, and thereby reduced the effects of economic misfortune on health and well-being.

Another striking example of the complex relations between poverty, nutrition and public health has been recorded by M'Gonigle and Kirkby (1936). Their observations were made at Stockton-on-Tees on social groups at the bottom of the economic scale, a large proportion of the wage-earners concerned being unemployed. In 1927 an unhealthy slum (Housewife Lane) was demolished and the population was moved into a modern housing estate. It was possible to keep separate figures for mortality rates for this population both before and after the move and to compare them with a control population remaining in a slum (Riverside area).

Table 49, 2 shows that the move from the unhygienic slum into the apparently healthy environment of the new housing estate did not result in an improvement in health, but was unexpectedly followed by an increase in the death-rate of the people above both their former level and the level of their neighbours who remained in the Riverside slum. The estate itself could not be blamed for the higher mortality, the houses being well constructed and possessing good sanitary arrangements. The deterioration in health was directly attributed to an increase in the rents in the new estate. This of necessity caused a corresponding reduction in the amount of money available for buying food. The income expended on food purchases fell 11d./head/week as compared with the controls in

TABLE 49, 2. *Mortality in Stockton-on-Tees*

(Standardised quinquennial death-rate : deaths per 10,000 population)

	Total for the borough	Housewife Lane population	Riverside population
1923-27 . . .	12	23 (in a slum)	26 (in a slum)
1928-32 . . .	12	34 (in a housing estate)	23 (in a slum)

the slums. The benefits to health, which might have resulted from the improved hygiene of the external environment, were more than neutralised by the higher rents, which reduced the money available for the purchase of food.

These brief summaries of the main conclusions from the books by Orr, and M'Gonigle and Kirby serve to show in outline the striking effect of poverty on health. They stress that, amongst the manifold evils of poverty, the inability to obtain sufficient food is predominant and they illustrate what can occur in a comparatively wealthy country such as pre-war Great Britain. In other parts of the world the relationships are even more striking and are often such a feature of everyday life that both the people and government become accustomed to the facts and blind to the consequences. This is well illustrated in two surveys by Mitra (1941), carried out in urban and rural India which demonstrate with detailed figures the close connection between income and food consumption.

Lack of kitchen facilities and equipment

Although as M'Gonigle and Kirby showed, good housing and other amenities can in no way mitigate the evil consequences of lack of money to purchase food, yet inadequate housing and kitchen facilities may prevent families from obtaining a satisfactory diet, even if sufficient money is available. In Great Britain during the last world war clinical evidence of malnutrition was not infrequent amongst urban families whose incomes were adequate to purchase sufficient food. The cause of this malnutrition was attributed to overcrowding and bad housing. Many families were living in single rooms, often sharing totally inadequate cooking apparatus, and without larders or space for food storage. Under such conditions domestic chaos is inevitable ; there is neither the leisure, the apparatus nor the space to prepare proper meals. Here we have the exact opposite to the situation in Stockton-on-Tees. It is clear that to provide adequate nutrition for its members, a family must have both an adequate house and an adequate income. If either of these is lacking then malnutrition may arise ; however satisfactory the one, it cannot compensate for an inadequacy of the other.

Lack of leisure

An important secondary cause of inadequate nutrition may be lack of leisure. Proper nutrition demands time for the preparation of meals and for their consumption. For instance, in industrial communities many people live far away from their place of work and must spend much time in travelling to and from their homes. They may leave home at an early hour without a proper breakfast. Many workers are still not provided with adequate breaks for their meals and suitable places for eating them. Restaurants and canteens may be so inadequately staffed that they are unable to provide meals in the time available to their patrons. A feature of rationing and food restrictions in the post-war world was the queue, often for the little extras that added a touch of interest to an otherwise monotonous diet. The time that a housewife spends in a food queue is time wasted, which might have been spent in the better preparation of meals.

By reason of their infirmities the elderly sometimes have not the energy required for shopping under modern conditions. They may thus be prevented from getting the best foods at the lowest price. Difficulties of this nature are a very real cause of underfeeding amongst some of the old to-day.

Lack of transport

Another cause of unequal distribution of food leading to malnutrition and underfeeding is inadequate means of transport. Now that enormous numbers of the world's population live far from the land producing their food, the food has to be taken to the people in ships, in trains, in lorries and carts. Shortage of these means of distribution may determine food supplies. In time of peace, transport has usually been available in sufficient quantity, but economic barriers preventing its full use have presented more formidable problems.

Following a major natural disaster such as fire, flood or earthquake destroying the food supply of a large group of people, the most urgent measure needed may be the collection and marshalling of sufficient transport to bring in food from outside. Similarly, the havoc of war may separate a large community from its usual source of food. In 1945, for instance, 5 million people in the mountains of Yugoslavia were isolated from the rich food-producing plains by the war-time destruction of road and railway bridges, lorries and rolling stock. Only by the construction of temporary bridges and the assembly of transport of every kind was a major famine averted. In Bolivia there is much subnutrition amongst the population who live on the *altiplano* where most of the tin and other mineral wealth is to be found. They are separated from rich underdeveloped agricultural land on the plains by precipitous mountains and gorges through which no modern roads or railways run.

Ignorance

This is delicate ground. Much ignorance of the general principles of good nutrition exists in all countries of the world. In many of the less-developed countries lack of knowledge of the high nutritional requirements of growing children results in an appreciable incidence of undernutrition and malnutrition even in areas where food supplies are adequate in quantity and quality. Improvements in the quality of the diet of many people can be effected by education, and particularly by the education of older girls in schools—the future housewives. But throughout the world poverty is more important as a cause of inadequate nutrition than ignorance.

Important points on which education is frequently needed include proper methods of cooking vegetables, the nutritional value of fish, the deleterious effects of overmilled cereals, the value of vegetable gardens, and the special needs of children for milk, cod-liver oil and fruit juices.

Religious customs

The effect of these on food habits may be important. In simple rural communities, all religions commemorate important events in the lives of saints and prophets, and the ceremonies associated with marriage and death are celebrated either by feasts or fasts. The feasts often provide an excuse for the slaughter of an animal and the consumption of much extra animal protein. A variety of other delicacies may be set aside for use on these occasions only. Feasts are of value in supplementing a monotonous and inadequate day-to-day diet and in many communities dietary surveys, which omit such occasions, may be misleading. Fasts are generally fewer in number, and there is no evidence that an occasional day's fast ever did a healthy individual any harm. They may be of benefit to the richer members of a community, but impair the health of people whose day-to-day food consumption is limited by inadequate supplies or low purchasing power. During Ramadan, which lasts for one lunar month in every year, many orthodox Muslims neither eat food nor drink water between sunrise and sundown. Even if the food intake during the hours of darkness is satisfactory, lack of sleep by night and lack of water by day make it difficult for a man to maintain working efficiency throughout a long and hot day, for four weeks, under these conditions. Whatever the religious and spiritual significance of the fast may be, most people who have had to work with Muslims during Ramadan will agree that it gives rise to losses of stamina and working efficiency.

Religions also enforce many food taboos. Jews and Muslims are forbidden the flesh of the pig, but more important is the Hindu prohibition of the consumption of beef and of the slaughter of cattle. In India the health of the cattle is the crux of the whole economic system. They plough the land, fertilise the soil, carry the crops to market, provide milk for the family and fuel for the hearth. A well-fed, healthy cattle population is a *sine qua non* of a well-fed and prosperous human community. The exact origin of the taboo on the slaughter of cattle is uncertain, but it was not a part of the Dravidian and earliest Hindu cultures. No doubt the prohibition arose as a practical expediency under certain acute local circumstances and thereafter received general sanction. A ban on slaughtering cattle might have little effect if abundant cattle fodder were available, enabling the community to pension off and preserve the older animals no longer useful to man. In modern India such conditions do not exist. The pressure on the land by both man and beast is great; sufficient food is at present grown for neither. It has been estimated that half of India's enormous number of cattle have no economic value. They can neither provide milk nor pull the plough, but use up land needed for the production of human food.

In tribal Africa many food taboos have been described (Trant, 1954), which are often strict during pregnancy and lactation. These taboos may reduce the nutritional value of a mother's diet and so affect her health and that of her child. An understanding of these taboos is important for the nutritionist, who may be wise to consult an experienced social anthropologist.

CHAPTER 50

THE ASSESSMENT OF NUTRITIONAL STATUS

THE attitude of governments to nutrition is interesting and important. Most modern states have arisen by a slow process of evolution—occasionally hastened by revolution—out of simple agricultural communities. The land was usually able to provide sufficient food to meet the people's needs. Whether a man and his family obtained adequate food depended on the ingenuity and industry with which he cultivated his land. Governments were not particularly interested in food production, except in so far as agricultural produce could be taxed or when a major disaster threatened a widespread famine.

The industrial revolution at first did not change this attitude. Each wage-earner was expected to earn by his own efforts enough money to purchase on a free market sufficient food for his family. Gradually it was realised that many were unable to do this and that widespread malnutrition was present in the industrial populations of all countries. In Great Britain the discovery that a large proportion of the recruits who volunteered for the South African War (1898-1901) were physically unfit for military service, and the realisation that poor diets were responsible for much of this unfitness, aroused widespread interest and dismay. It is now recognised in most industrial countries that if an urban population is to be sufficiently healthy to enable men and women to be effective producers of manufactured goods and also to be able-bodied members of the armed services, governmental responsibility for planning and co-ordinating national food policies is essential.

In some predominantly agricultural countries the population has multiplied and outgrown its present agricultural resources; nutrition has accordingly become a national problem. Such countries obviously require national nutrition policies under competent governmental direction.

In the world to-day most national governments and many local governmental agencies have active nutrition programmes: these are discussed more fully in the next chapter. Clearly the need for such programmes and their efficacy can only be determined by periodic assessments of the nutritional status of the people. Accurate assessments should be the foundation of all governmental food policies. Unfortunately measurements of nutritional needs and deficiencies have never been easy and always require the exercise of considerable judgment. No rule-of-thumb method is available. Five different lines of investigations have been used. These are :—

1. Clinical examinations.
2. Biochemical and other laboratory findings.

3. The study of vital statistics.
4. The study of anthropometric data.
5. Dietary surveys.

Each of these must now be considered in detail.

1. CLINICAL EXAMINATIONS

The distinction between the well and the poorly nourished might appear to present no difficulties. A well-nourished person is alert and active with firm muscles, bright eyes and a smooth, elastic skin ; the poorly fed person is inert and lethargic, with flabby muscles and perhaps a rough, dry skin. In practice there are so many ill-defined grades between the obviously well-nourished and ill-nourished, that assessment is very difficult. Muscle tone and posture are not readily susceptible to measurement, nor are they closely related to nutritional status. Clinical impressions are often erroneous, because the judgment of even an experienced physician is subject to a high degree of observer error. Jones (1938) showed that even experienced school medical officers were unable to grade British school children consistently at a single inspection. There were many and important differences of grading of the same child by different physicians, and even by the same physician on different days. Clinical impressions are an uncertain guide to nutritional status except under famine or near-famine conditions, when gross subnutrition is evident.

In Part III the major nutritional diseases and also the lesser stigmata of malnutrition were described. Accurate recording of the incidence of these conditions in a population is a most valuable part of a nutritional survey.

Whenever possible, and particularly in the less-developed countries where undernutrition and malnutrition are common, the incidence of nutritional disease should be determined by examining a satisfactory sample of the population by economic class, occupation, age and sex. Pre-school children, their mothers and elderly people living alone are particularly liable to deficiency diseases and are overlooked by surveys of functional groups such as school children, factory workers, farmers or business men. The latter types of survey are easier to conduct. Such comprehensive clinical surveys should be carried out in the home, most usefully in conjunction with a dietary, social or economic survey.

In times of food shortage or famine the clinical state of the people walking about in the streets may be no guide. Those weak with subnutrition may be unable to leave their homes. This source of error misled some of those who accompanied the liberating armies into Holland in 1945 into underestimating the extent of the famine.

A real difficulty arises in recognising minimal signs of nutritional disorders. A good hand-lens is a valuable aid in examining the eyes and skin, but it is important not to use it for observing and recording minor changes that are not pathological. A conjunctiva may be a little dry, a skin a little rough, a mucocutaneous junction a little uneven. Is xerophthalmia, hyperkeratosis or angular stomatitis present? It is usually best, if in doubt, not to record such equivocal signs. Systems of grading the severity of such signs have been used and some have proved very valuable in practice (Nicol, 1952).

Table 50, 1 shows a record card designed by FAO/WHO (1959) which has been found useful for recording results in the field. The card can be

TABLE 50, 1. *Clinical Nutrition surveys*

RECORD CARD

Number ....

Name ....

Father's name ....

Mother's name ....

Address ....

....

Date ....

Date of birth or age ....

Sex ....

Weight .... *Height* ....

Arm circumference ....

Pregnancy ....

Lactation ....

Hair—
- Depigmentation
- Pluckability
- Texture

Eyes—
- Bitôt's spots

Mouth—
- Angular stomatitis
- Glossitis
- Hypertrophic and hyperæmic gums
- Pallor of buccal mucous membranes
- Teeth—
  - Total number of teeth present ....
  - Number of carious teeth ....

Thyroid—
- Goitre—
  - Group 1.—Palpable, not visible
  - Group 2.—Palpable, visible, small size
  - Group 3.—Palpable, visible, large size
  - Nodules

Blood—
- Hæmoglobin level (specify method)

Skin—
- Œdema
- Follicular hyperkeratosis (symmetrical) posterior aspect of forearms
- Pigmented areas, neck, chest, forearms, hands, feet

Skeleton—
- Rickety rosary
- Harrison's sulcus
- Widening of epiphyses of wrists and malleoli
- Deformed lower limbs—
  - (*a*) Bandy legs
  - (*b*) Knock knees

Other signs—

Name of observer ....

Appointment ....

....

A tick should be marked on the card against all positive findings and the part of the body examined.

used by non-medical staff, if specially trained and under the supervision of a doctor.

On the medical evidence alone, it is usually possible to divide the families into three groups :—

1. Those families in which every member is obviously fit.
2. Those in which at least one member (usually the mother or a young child) has unequivocal signs of nutritional failure.
3. The rest (often the large majority) in which one or more members has some clinical defect, not necessarily due to malnutrition, but sufficient to exclude the family from Group 1.

A careful subsequent comparison between the dietary and other data from the families in Group 2 with those in Group 1 can yield valuable information about the chief causes of nutritional failure in the community concerned. By this method Meiklejohn and Williams (unpublished) showed that malnutrition in five British industrial communities during the period of stringent rationing in 1941-43 was due not so much to the lack of food supplies but to the problem of large families living on low wages in overcrowded conditions.

Detailed clinical examination of individual children in the absence of established physical signs is for the most part a profitless method of assessing nutrition, but all experienced nutritionists take every opportunity to observe groups of children at play. To see active and vigorous games in a school playground during a break in the lessons is to know that most of the children are not malnourished.

2. BIOCHEMICAL AND OTHER LABORATORY FINDINGS

The difficulties and uncertainties of clinical assessments of nutrition have been described in the preceding section. They have long been known. When the vitamins were discovered and modern methods of biochemistry developed, there began a vigorous search for a chemical measure of nutrition ; blood and urine were analysed for their vitamin content and for the presence of intermediary metabolites known to accumulate in deficiency diseases. The results have been for the most part disappointing. It is true that in many nutritional disorders there are clear-cut biochemical changes. These have been discussed in the chapters on the vitamins and various deficiency diseases. Yet unequivocal biochemical evidence of a nutritional disorder seldom precedes the clinical evidence. Biochemical changes in the blood, like observable clinical changes, do not develop abruptly in clear-cut stages but by a series of gradations. Biochemical methods have a real place in unravelling difficult diagnostic problems in a hospital, especially if the deficiency disease is conditioned by some other disease, *e.g.* of the alimentary tract. In field studies they are useful only if carried out on a scale sufficiently large for statistical treatment of the data.

It can be stated confidently that the single most important piece of laboratory equipment needed for a nutritional survey is a good hæmoglobinometer. Only with this piece of apparatus is it possible to judge the degree of nutritional anæmia present in a community. Other more elaborate and costly biochemical equipment may provide useful information, but is not essential.

Similar disappointing results have followed physiological laboratory tests for nutritional status, as carried out in field surveys. The discovery that night blindness was a common feature of vitamin A deficiency led to the elaboration of tests for night vision. Many of these have fallen into disuse as it was found that they were profoundly affected by emotional and other factors. However, the apparatus designed by Wald (1941) and modified by Dow and Steven (1941) appears to have overcome these difficulties and can be recommended as a practical and reliable test for the diagnosis of vitamin A deficiency.

Much time has been spent in attempting to measure the properties of human muscle and to correlate the results with nutritional status. Large numbers of measurements have been made of the power, speed, endurance and co-ordination of various muscular movements. Unfortunately, in such tests the influence of psychological and emotional factors is so great, and impossible to control adequately, that the methods have fallen into disuse.

3. THE STUDY OF VITAL STATISTICS

Most countries keep at least some vital statistics and from them it is usually possible to draw certain inferences about the nutrition of the people. The most used for this purpose has been the infant mortality rate (the number of babies dying in the first year of life per 1000 live births). Table 50, 2, prepared by the World Health Organization, shows infant mortality rates for different countries. There is no doubt that the lower figures come from the best-nourished populations and *vice versa.*

It has been suggested that the neonatal mortality (deaths of infants under 1 month per 1000 live births) and the stillbirth rate may give a more precise index of nutrition. Table 50, 3 gives these figures for England and Wales and for Scotland from 1933 to 1960. Many factors determine survival or death just before and after birth (the perinatal mortality), *e.g.* the nutritional status of the mother, the genetic or constitutional make-up of both mother and child, the degree of exposure to infections and the standard of medical care available. Sir Dugald Baird (1960) has analysed recent trends in perinatal mortality in England and Wales and in Scotland. He concludes that the war-time fall in the rates was due to the special supplementary rations which pregnant women received. This strongly suggests that the quality of the diet consumed during pregnancy has an important influence on the outcome of pregnancy. Fig. 50, 1, taken from his paper, shows regional variations in 1957 in perinatal mortality rates ; the districts in black with the highest rates are

TABLE 50, 2. *Infant mortality*, 1900-52 ; *deaths of infants under* 1 *year of age per* 1000 *live births in same year*

	1901-5	1921-25	1952	1960
Australia . . .	97	...	24	20
Belgium . . .	148	...	35	31
Canada . . .	...	98	38	27
Ceylon . . .	171	...	78	58 (1959)
Chile	264	...	134	120 (1959)
Denmark . . .	119	...	29	22
England and Wales .	138	...	27	22
Finland . . .	131	...	32	21
France . . .	139	...	41	28
India	...	206	116 (1951)	...
Ireland . . .	94	...	41	29
Israel	...	126	39	31
Italy	167	...	64	44
Malta . . .	...	270	72	38
Netherlands . .	136	...	23	16
New Zealand . .	75	...	24	20
Northern Ireland .	108	...	39	27
Portugal . . .	144	...	94	78
Scotland . . .	120	...	35	26
Spain . . .	172	...	54	35
Sweden . . .	91	...	20	17
Switzerland . .	134	...	29	21
U.S.A. . . .	...	74	29	26

Data from WHO (1961).

TABLE 50, 3. *Perinatal mortality in Great Britain*, 1933-60

Year	Deaths of infants under 1 month per 1000 live births (neonatal)		Stillbirths per 1000 total births	
	England and Wales	Scotland	England and Wales	Scotland
1933 . .	32	38	41	Not available
1939 . .	28	37	38	42
1945 . .	25	29	28	33
1950 . .	19	23	23	27
1955 . .	17	20	23	25
1956 . .	17	19	23	24
1957 . .	16	20	22	24
1958 . .	16	19	22	23
1959 . .	16	19	21	22
1960 . .	16	18	20	22

South Wales and the Glasgow area. These heavily industrialised regions have not been so prosperous as London and the home counties which have the lowest perinatal mortality rates. These differences are very similar to those of other indices of poor nutrition and living conditions.

The manifestations and effects of malnutrition are well known to be severe in toddlers (children aged 1 to 4 years). Wills and Waterlow (1958), as a result of studies in the West Indies, suggest that the toddler death-rate is a useful index of malnutrition. In the nineteenth century in Great Britain, with many toddlers living in slum homes and improperly fed, the mortality rates were sometimes up to 100 deaths/1000 aged 1 to 4 years. In 1960 the figure was below 4 and many of these deaths were due to accidents. Wills and Waterlow record figures of toddler mortality rates between 12 and 35 in various parts of the West Indies. Malnutrition would certainly have contributed to many of these deaths.

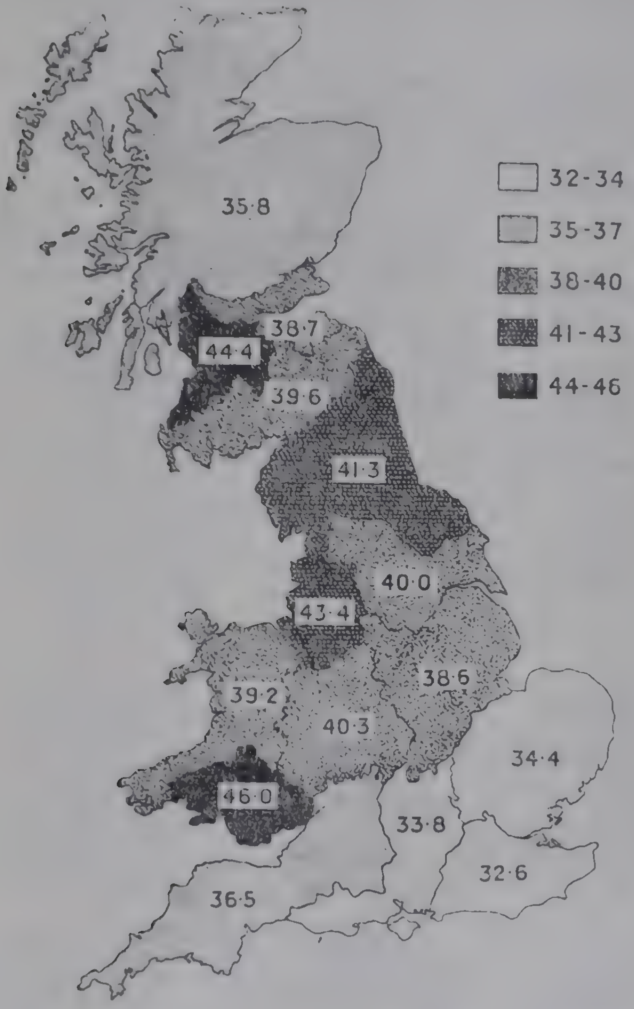


FIG. 50, 1. Perinatal mortality rates. Standard regions of England, Wales and Scotland, 1957.

Before the introduction of antibiotics, infectious diseases, such as measles, whooping-cough and pulmonary tuberculosis, were major causes of death. Chances of survival from these diseases were certainly reduced if the nutritional state of the patient was poor. Death-rates from these infectious diseases have been used in the past as indications of the nutritional status of a population. They are, however, of little practical value in most countries at the present time, because of the use of specific remedies either against the diseases or their complications.

If in any country, province or city the infant and toddler mortality rates, the neonatal mortality rate and the stillbirth rate are all falling, then it can be inferred that the general level of nutrition of the people is very probably improving. On the other hand, a rise in any one of these rates should suggest the possibility that there has been a serious decline in standards of nutrition. In some countries the maternal mortality rate is also a useful index of nutrition.

In times of food scarcity, daily, weekly and monthly crude death-rates may give valuable information about changes from conditions of hardship to conditions of famine. During the Second World War the Dutch had 4 years of food shortage and scarcity. These were very unpleasant but did not constitute a major hazard to health. They were followed from December 1944 to April 1945 by 5 months of real famine. Table 50, 4 shows the effect of these changes on crude death-rates in some of the principal cities of Holland. In Amsterdam, Rotterdam and the Hague during the worst week of the famine, crude deaths of about 40 per 1000 (calculated on a yearly basis) were recorded. Such figures proved extremely useful to famine administrators in gauging the extent of the disaster and the success of relief measures.

TABLE 50, 4. *Number of deaths in four cities in Western Holland* (*Burger et al.*, 1948)

City	Population	Number of deaths in the first 6 months of			Number of deaths per 1000 inhabitants calculated as mortality in 1 year		
		1939	1944	1945	1939	1944	1945
Amsterdam .	800,000	3655	4393	9735	9·2	11·3	25·2
Rotterdam .	640,000	2616	3260	7827	8·5	10·7	25·8
The Hague .	520,000	2419	2940	6458	9·7	13·0	28·7
Utrecht . .	170,000	776	1120	2065	9·3	13·0	24·3

Had similar crude death-rates been available from rural Bengal early in 1943, the extent of the famine there would have been realised sooner, relief organisations would have started earlier and the mortality figure of 1½ million from starvation might have been much less.

4. THE STUDY OF ANTHROPOMETRIC DATA

Heights and weights

If children do not get sufficient food, they fail to grow properly. Similarly, adults without enough to eat lose weight and those who overeat gain weight. The weighing machine is a useful and accurate tool for investigating nutritional status. Measurements of weights of adults and of large groups of children at various ages have been used as an index of nutritional status, and have proved very valuable when correctly interpreted. The weighing machine has also been widely used in school medical services and at child health clinics as a simple diagnostic tool for the purpose of screening children who may be undernourished. By these means the detection of subnutrition may be facilitated and those found to be underweight can be subjected to detailed medical examination and—if necessary—provided with extra food.

It is important to realise that other factors besides food intake determine weight, notably constitutional or genetic make-up. There are tall, thin, light people and short, thick-set, heavy individuals who may each be equally healthy ; the weighing machine alone cannot determine their relative nutritional status. Other physical measurements—and particularly height—are useful.

There are certain difficulties involved in the use of such a simple piece of apparatus as a weighing machine. Every balance needs regular checking and, if necessary, re-calibration. Lever balances made by firms of repute are very reliable and a yearly check is all that is necessary. Spring balances are most unreliable and, if used regularly, need repeated checks. Indeed they cannot be recommended for accurate work. It is seldom practical to weigh people naked ; a correction is usually needed for the articles of clothing worn. They may vary greatly from season to season and according to fashion. Men usually wear heavier underclothing than women. A rough estimate of a man's clothes in Great Britain without shoes or jacket is about 6 lb. Shoes and jacket usually weigh about 4 lb. more. Women's shoes and clothes usually weigh about 6 lb. In comparing individual weights with standards, it is important to make certain that the standards were obtained under comparable conditions of clothing.

Height should be measured against a flat surface and the subject must stand as upright as possible without raising the heels from the ground. A sliding headpiece is necessary for accurate work. It is impossible to record standing height in infants and very young children. In older children and adults the measurement is subject to considerable daily variation, and is usually greater in the morning than in the evening, due to effects arising from fatigue and faulty posture. For these reasons measurements of recumbent length are better, especially for children up to 2 years of age. Over the range 110 to 180 cm. (42 to 71 in.) recumbent length exceeds height by an average of 0·5 cm. (0·20 in.) for boys and 1·1 cm. (0·42 in.) for girls.

In children it is necessary to record age accurately. In some parts of the world, children and their parents have no recollection of their age and this fact may make records of weight for age useless. So far, no easy way round this difficulty has been found.

As in all other methods of nutritional assessment, accurate sampling is necessary. Most children attend schools and it is usually easy to get a fair sample of the child population. But it is always difficult to get a random sample of an adult population. For instance during the food shortages in some central European cities after the Second World War, the occupying military authorities thought that a regular sample of the weights of the civilian population would provide an index of the adequacy of civilian food supplies and thus be a measure of the success of food policies. In this they were probably right. But they proceeded to station a sergeant and a military orderly with a weighing machine at vantage points in the cities with instruction to weigh every tenth passer-by. These records, on examination, were found to produce data heavily biased numerically in favour of the female sex and the age group 15 to 25 years.

TABLE 50, 5. *Mean lengths and weights of infants and pre-school children (Edinburgh* 1951-53)

Age	Length			Weight		
	Mean		S.D.	Mean		S.D.
	cm.	in.	cm.	kg.	lb.	kg.
BOYS						
Birth	50·9	20·0	1·9	3·4	7·5	0·40
2 weeks	51·7	20·3	2·0	3·4	7·5	0·39
3 months	60·2	23·7	1·9	5·8	12·9	0·68
6 months	66·7	26·2	1·8	7·9	17·4	0·77
9 months	71·2	28·0	2·0	9·2	20·4	0·85
1 year	75·1	29·6	2·3	10·3	22·8	1·08
2 years	86·4	34·0	2·8	12·2	27·0	1·18
3 years	95·9	37·8	3·6	14·3	31·5	1·43
4 years	103·0	40·6	3·7	16·2	35·6	1·71
5 years	109·5	43·1	4·6	18·3	40·2	2·06
GIRLS						
Birth	49·5	19·5	1·9	3·3	7·3	0·45
2 weeks	51·0	20·1	2·0	3·3	7·3	0·43
3 months	58·8	23·2	1·9	5·5	12·0	0·60
6 months	65·0	25·6	1·9	7·4	16·4	0·79
9 months	69·6	27·4	2·1	8·7	19·2	0·93
1 year	73·9	29·1	2·6	9·8	21·7	1·07
2 years	85·5	33·7	3·1	11·6	25·7	1·34
3 years	93·8	36·9	3·5	13·8	30·4	1·63
4 years	101·6	40·0	3·8	15·7	34·5	1·81
5 years	108·9	42·9	3·7	17·9	39·4	1·94

From data of THOMSON (1954 and 1955).

If these technical details can be overcome, as is usually possible, there remains the much more fundamental difficulty of the choice of proper standards for comparative purposes. Owing to varying genetical and racial factors and perhaps environmental conditions, no general standards can be of universal application. Local standards must be made and, if these are available, comparisons are very valuable. Tables 50, 5 and 6

TABLE 50, 6. *Mean lengths and weights of school children (Edinburgh* 1951-53)

Central age (years)	Length			Weight		
	Mean		S.D.	Mean		S.D.
	cm.	in.	cm.	kg.	lb.	kg.
	BOYS					
5·5	109·3	43·0	4·9	19·0	41·9	2·1
6·5	115·4	45·4	6·2	21·1	46·3	2·8
7·5	122·1	48·1	5·8	23·8	52·5	2·6
8·5	125·2	49·3	5·1	25·2	55·6	2·8
9·5	130·5	51·4	5·9	27·5	60·6	3·3
10·5	136·0	53·5	6·0	30·2	66·8	3·8
11·5	141·3	55·6	6·7	33·4	73·6	5·1
12·6	148·1	58·3	7·9	37·0	81·6	5·6
13·5	152·5	60·0	8·5	42·0	92·6	7·8
14·5	159·4	62·8	9·1	46·0	101·4	7·8
15·4	167·2	65·8	8·7	54·6	120·4	8·9
16·6	173·5	68·3	8·3	60·6	133·6	8·4
17·5	173·7	68·4	6·9	62·5	137·8	9·7
	GIRLS					
5·6	110·4	43·5	5·0	18·9	41·7	2·2
6·5	115·6	45·5	6·0	20·8	45·9	3·5
7·5	121·1	47·7	5·2	23·3	51·4	3·2
8·5	125·4	49·4	6·3	24·8	54·7	3·1
9·5	130·2	51·3	6·1	27·9	61·5	4·3
10·5	135·4	53·3	7·2	29·6	65·3	4·2
11·5	141·4	55·7	7·1	33·8	74·5	5·1
12·5	148·4	58·4	7·2	38·9	85·8	6·0
13·5	155·1	61·1	7·4	44·8	98·8	7·5
14·5	157·1	61·9	7·5	48·1	106·0	8·4
15·4	162·1	63·8	5·3	52·9	116·6	7·8
16·5	162·8	64·1	5·3	54·6	120·4	6·6
17·5	164·3	64·7	6·7	57·0	125·7	8·2

From data of PROVIS & ELLIS (1955).

give data for infants, pre-school children and school children obtained in Edinburgh a few years after the Second World War. The data are for nude weight and recumbent length. The younger children were weighed without clothes. Those who were maturing sexually were given a surgical gown and the weight of the gown subtracted from the recorded weight. The tables provide standards of average heights and weights of a well-fed population of European children and adolescents.

Records of heights and weights of children are of no use unless they are carefully interpreted. It is often useful to plot the height against the weight, either of single children or average figures of small groups, on to a piece of graph paper on which standard heights against standard weights have previously been plotted. It can then easily be seen how the recorded weight compares with the standard weight for the recorded height. If the child's weight is below the standard for his height, this indicates a subnormal physique. Since the assessment of this ratio is independent

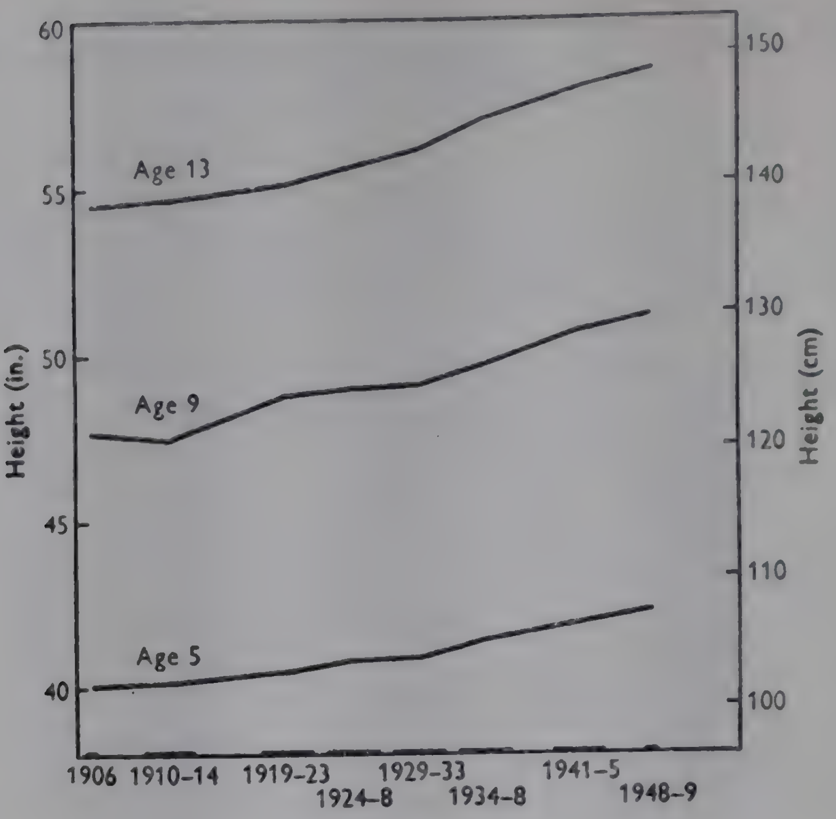


FIG. 50, 2.

Secular changes in growth of Glasgow schoolboys. Average values of height of age groups 5, 9 and 13 years for the periods indicated.

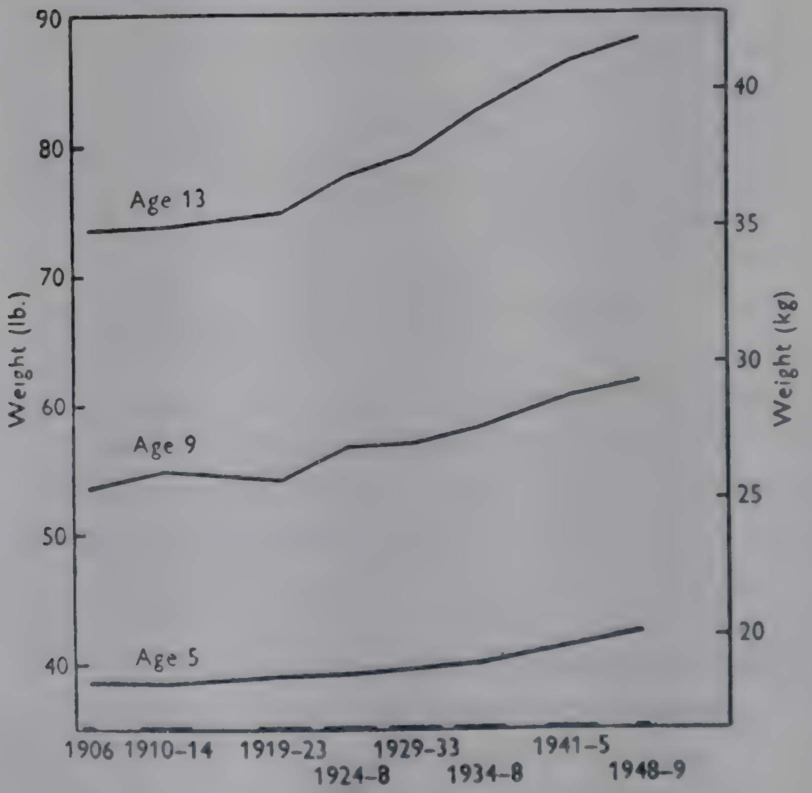


FIG. 50, 3.

Secular changes in growth of Glasgow schoolboys. Average values of weight of age groups 5, 9 and 13 years for the periods indicated.
From WEIR (1952).

of age, it is often valuable in those parts of the world where children's ages are not accurately known.

Many British cities have records for the past 50 years of heights and weights of their school children at selected ages. Some data for Glasgow (Weir, 1952) are shown in Figs. 50, 2 and 3. The genetic make-up of the population has been unchanged and there can be little doubt that the figures record a progressive increase in the growth rates of individual children associated with improved nutrition.

Scott (1961) has written a valuable report on recent measurements of London school children. In this he shows that in the last decade the average height and weight of school children continued to increase. Associated with this is a significant earlier onset of puberty in both girls and boys.

Although many records of heights and weights of Asiatic children are available and a few of African children, none are probably of much general value as standards. Conditions vary widely in these continents and local authorities must make their own records which can serve as a measure for future changes. Systematic measurements with a good statistical analysis have been made in Ceylon (Gunasekera & Mahadeva, 1957).

For adults Table 50, 7 gives figures for *average* height and weight at various ages. The figures were obtained as a result of an investigation called ' The Build and Blood Pressure Study, 1959.' This study (Lew, 1960, 1961) combines the experiences of twenty-six large life insurance companies in the United States and Canada between 1935 and 1954. It involved the observation of nearly five million insured persons over periods up to 20 years. These insured persons resembled the general population of North America closely because they included a sizeable population of wage-earners and a representative portion of the later immigrant stocks. Measurements were made with the subjects wearing *indoor clothing and shoes*. The clothing was estimated to weigh 7 to 9 lb. for men and 4 to 6 lb. for women. Heels added about 1 in. to the height of men and 2 in. to the height of women.

Table 50, 8 gives figures for *desirable* height and weight. This table has been constructed by the Metropolitan Life Insurance Company (1960) and is their part of ' Build and Blood Pressure Study, 1959.' The *desirable* weights given in Table 50, 8 are those which have been found to be associated with the lowest mortality. The death-rate in overweight persons is higher than in those of *average* weight and the death-rate in persons of *average* weight is higher than those of *desirable* weight. Hence in clinical practice the aim should be to see that as far as possible patients should not exceed *desirable* weight.

The table for *desirable* weights differs from the table for *average* weights in that there is no correction for increasing age. *Desirable* weights are subdivided into those for persons with small, medium and large frames. This division is based on various anthropometric studies including width and depth of chest and hip width, but the exact criteria used have not

TABLE 50, 7. *Average weights for men and women*

According to height and age

Height (in Shoes) *	Weight in pounds (in indoor clothing)					
	Ages 20-24	Ages 25-29	Ages 30-39	Ages 40-49	Ages 50-59	Ages 60-69
			Men			
5 ft. 2 in.	128	134	137	140	142	139
5 ft. 3 in.	132	138	141	144	145	142
5 ft. 4 in.	136	141	145	148	149	146
5 ft. 5 in.	139	144	149	152	153	150
5 ft. 6 in.	142	148	153	156	157	154
5 ft. 7 in.	145	151	157	161	162	159
5 ft. 8 in.	149	155	161	165	166	163
5 ft. 9 in.	153	159	165	169	170	168
5 ft. 10 in.	157	163	170	174	175	173
5 ft. 11 in.	161	167	174	178	180	178
6 ft. 0 in.	166	172	179	183	185	183
6 ft. 1 in.	170	177	183	187	189	188
6 ft. 2 in.	174	182	188	192	194	193
6 ft. 3 in.	178	186	193	197	199	198
6 ft. 4 in.	181	190	199	203	205	204
			Women			
4 ft. 10 in.	102	107	115	122	125	127
4 ft. 11 in.	105	110	117	124	127	129
5 ft. 0 in.	108	113	120	127	130	131
5 ft. 1 in.	112	116	123	130	133	134
5 ft. 2 in.	115	119	126	133	136	137
5 ft. 3 in.	118	122	129	136	140	141
5 ft. 4 in.	121	125	132	140	144	145
5 ft. 5 in.	125	129	135	143	148	149
5 ft. 6 in.	129	133	139	147	152	153
5 ft. 7 in.	132	136	142	151	156	157
5 ft. 8 in.	136	140	146	155	160	161
5 ft. 9 in.	140	144	150	159	164	165
5 ft. 10 in.	144	148	154	164	169	†
5 ft. 11 in.	149	153	159	169	174	†
6 ft. 0 in.	154	158	164	174	180	†

* 1-in. heels for men and 2-in. heels for women.
† Average weights not determined because of insufficient data.
Source : *Metropolitan Life Insurance Company* (1960).

been published. It is stated that ' as a rule of thumb,' if persons of any particular build kept their weight down to the *average* in the early 20's, it would be fairly close to the *desirable* weight at ages over 25.

The ' Build and Blood Pressure Study, 1959,' confirms anew the adverse effects of overweight on the health of adults, particularly men, as reflected by a significant rise in mortality with increasing degrees of overweight. It reveals that the average weight of men, particularly in

TABLE 50, 8. *Desirable Weights for Men and Women*

According to height and frame. Ages 25 and over

Height (in shoes) *	Weight in pounds (in indoor clothing)		
	Small frame	Medium frame	Large frame
		Men	
5 ft. 2 in.	112–120	118–129	126–141
5 ft. 3 in.	115–123	121–133	129–144
5 ft. 4 in.	118–126	124–136	132–148
5 ft. 5 in.	121–129	127–139	135–152
5 ft. 6 in.	124–133	130–143	138–156
5 ft. 7 in.	128–137	134–147	142–161
5 ft. 8 in.	132–141	138–152	147–166
5 ft. 9 in.	136–145	142–156	151–170
5 ft. 10 in.	140–150	146–160	155–174
5 ft. 11 in.	144–154	150–165	159–179
6 ft. 0 in.	148–158	154–170	164–184
6 ft. 1 in.	152–162	158–175	168–189
6 ft. 2 in.	156–167	162–180	173–194
6 ft. 3 in.	160–171	167–185	178–199
6 ft. 4 in.	164–175	172–190	182–204
		Women	
4 ft. 10 in.	92– 98	96–107	104–119
4 ft. 11 in.	94–101	98–110	106–122
5 ft. 0 in.	96–104	101–113	109–125
5 ft. 1 in.	99–107	104–116	112–128
5 ft. 2 in.	102–110	107–119	115–131
5 ft. 3 in.	105–113	110–122	118–134
5 ft. 4 in.	108–116	113–126	121–138
5 ft. 5 in.	111–119	116–130	125–142
5 ft. 6 in.	114–123	120–135	129–146
5 ft. 7 in.	118–127	124–139	133–150
5 ft. 8 in.	122–131	128–143	137–154
5 ft. 9 in.	126–135	132–147	141–158
5 ft. 10 in.	130–140	136–151	145–163
5 ft. 11 in.	134–144	140–155	149–168
6 ft. 0 in.	138–148	144–159	153–174

* 1-in heels for men and 2-in. heels for women.

NOTE.—Prepared by the Metropolitan Life Insurance Company (1960). Derived primarily from data of the *Build and Blood Pressure Study*, 1959.

the younger age groups (25 to 40), is higher than that of the similar age group a generation ago. On the other hand, women below the age of 40 tend to be lighter than those of the same age groups of 30 years ago. It is of significance that during this period the mortality of women has declined sharply, whereas the trend of mortality among men has been much less favourable. This valuable study clearly demonstrates that in the U.S.A. and Canada there are too many people who are overweight, and it draws attention particularly to the need of preventing overweight in men between 25 and 40 years of age. It also clearly shows the benefits of weight reduction in lowering the mortality of overweight people. Another important point brought out by the 1959 study is the demonstration of the evil effects of overweight in persons with minor disabilities, *i.e.* with pathological changes such as hypertension or albuminuria ' of a degree not sufficiently great to debar an applicant from obtaining standard assurance ' ; the mortality rate was increased by some 30 to 40 per cent. in overweight men with minor impairments as compared to overweight men with no known minor impairments.

In conclusion, the ' Build and Blood Pressure Study, 1959,' demonstrates clearly that overweight is one of the most important medical and social problems in America and Canada ; this is almost certainly true of other highly-developed countries. It focuses attention particularly on the advantages of being under the average weight and on the need for weight reduction in all overweight persons, particularly in young men below the age of 40.

We recommend that these new tables be used for assessing the nutritional state of adults both in clinics and in large surveys. They should replace the old American tables, which have been used in many parts of the world for over 50 years and have been reproduced in many medical textbooks. The old tables were based primarily on data collected in the nineteenth century and published as early as 1912 by the Metropolitan Life Insurance Company.

In Great Britain 60,000 of the civilian population were measured during the Second World War (Kemsley, 1952). Measurements were made with indoor clothing and footwear. To correct for these, deductions of 10 lb. in weight and 1 in. in height for men and 6 lb. and 1½ in. for women have been made in the published figures. In Canada 22,000 people were weighed and measured in 1953 (Pett, 1955). They were selected on a statistical basis from the fifty-nine regions of the country. Measurements were made in indoor clothing, but without footwear, by a trained staff. No corrections for clothing are made in the published data.

If the three sets of data are compared for the age group 20 to 25 and for both men and women, the U.S.A., British and Canadian figures are almost identical. There are, however, differences in the effects of age in the three surveys. In each there is evidence of what is popularly called a ' middle-age spread.' This was smallest amongst the British and largest amongst the Canadians. The food restrictions in war-time Britain may have reduced middle-age spread, though they did not affect the weight of young adults. On the other hand the large gains of weight amongst the people in prosperous Canada almost certainly reflect a high incidence of obesity.

Records of the heights and weights of Asiatics and Africans, as far as we know, have not been collected on a scale sufficiently large to justify their general use in assessments of nutrition.

Other anthropometric data

A vast amount of ingenuity has been expended on attempts to provide formulæ based on anthropometric measurements which will provide an index of nutritional status. The essential difficulty is, of course, that size and shape is determined in part by genetic make-up and in part by environmental factors, of which the nature of the diet is only one, albeit usually the most important one. Examples are Tuxford's (1942) index; cristal height (Leitch, 1951); arm, chest and hip (ACH) index (Franzen & Palmer, 1934; Aykroyd *et al.*, 1938); and the Wetzel grid. Each has been extensively tried out and, under certain circumstances, has proved useful though none of them has been widely accredited as an aid to nutritional diagnosis. In general it may be said that in the hands of the enthusiastic inventors the tools have been a means to provide useful information. Other workers have found them less satisfactory. Height, weight and arm circumference, accurately recorded and properly compared against suitable standards, will generally be sufficient in surveys designed to assess the nutritional status of a community. The devising of anthropometric formulæ and the testing of their usefulness is an occupation that has fascinated many able minds. If the techniques at present available have proved disappointing on the whole, this does not mean that the problem is insoluble—only that it is very difficult.

The search for methods of body measurement which will evaluate nutritional status continues (Brozek, 1956).

5. DIETARY SURVEYS

Quantitative information about the food eaten by a people or a community, if compared with physiological standards of human needs, has enabled assessments of nutrition to be made that have been widely used and proved both useful and practical. Data can be collected covering a whole nation, from families of different economic classes or from individuals of special age-groups or occupations. Each type of survey can provide valuable information. For sound government planning nation-wide data covering all socio-economic groups and age groups are required. In all cases the technique demands care and is time-consuming and exacting. Before describing the different methods and their difficulties, certain considerations common to all dietary studies require discussion.

A comparison can be made between the amounts of food consumed and a chosen physiological standard only when the data collected have been converted into quantities of calories, carbohydrate, protein, fat, minerals and vitamins. This involves the use of food tables and here errors are inevitably introduced. The extent of these errors has been discussed in Chapter 16.

Another difficulty is to reach agreement on the physiological or other standards with which to compare the results of dietary surveys. In Chapter 15 some tables of recommended allowances of nutrients were set out and discussed. If repeated dietary surveys are carried out systematically in a country, it is possible to tell whether the quantity or quality of the food consumed is improving or declining. This information is often more useful than a comparison with a physiological standard, which must always be arbitrary.

National studies.—These are attempts to assess the total food supply of a whole nation or other large community. The basic data are the statistics of agricultural production and the statistics of the imports and exports of food. In this way it is possible to estimate total food supplies and, with a knowledge of the population, to calculate the average daily supply of the principal nutrients.

FAO collects national data on these lines and publishes them at regular intervals. Table 49, 1 (p. 693) records some of FAO's data. The errors involved in such surveys may be very great. In some countries figures both for agricultural production and population can be nothing more than intelligent guesses. This applies to almost all of Africa and to many Asiatic and South American countries. On the other hand in a small, well-organised country such as Denmark, the degree of accuracy of such statistics is high.

Another important error that arises in the use of such data is that they give no accurate measure of wastage of food. This has been discussed in Chapter 22. FAO usually makes allowances for losses in the wholesale trade and its figures are intended to describe the food available at the ' retail ' or shop level. It is, of course, important not to attempt to match such figures directly against a standard of physiological ' requirements.' Some further wastage after purchase is inevitable.

The value of national estimates of food consumption has often been called in question : the errors involved are obvious. Nevertheless, an intelligent study of the figures can reveal much that is important about the nutritional status of many countries. Successive World Food Surveys have brought out valuable trends. FAO has done a great service in producing this information, without which the main purpose of the organisation could not be achieved—namely the improvement of human nutrition by scientifically planned agriculture.

Family surveys.—Most surveys have the family as the basic unit. A trained investigator with the co-operation of the housewife attempts to measure all the food consumed by a family over a period of time, usually a week. A log-book is kept for each family. The investigator visits the housewife at the start of the survey and weighs all the food in her stores. Each day, either the investigator or the housewife weighs all the food purchased and enters this in the log-book. The food wasted is also weighed and entered. At the end of the survey period all food remaining in the store is weighed. Thus all the food eaten in the household is recorded. The age, sex and occupation of the members are also noted.

The number of visitors eating occasional meals and the number of meals eaten outside the home by members of the family are also noted and arbitrary corrections made for them. In calculating the results, daily averages are sometimes expressed in terms of ' man values ' or consumption units. A scale of man values (Table 50, 9) prepared by the League of Nations in 1936 has been much used. Many people prefer to set out the results on a *per capita* basis and this is now the practice in most presentations of national food supplies and food consumption.

It must be emphasised that to conduct an accurate family dietary survey demands an exacting technique and experience on the part of the investigators. Here only a brief outline of the technique has been given. Further details can be found in excellent monographs by Thelma Norris (1949) and Emma Reh (1962), both produced under the auspices of FAO.

The family survey is useful for determining the food consumed by different economic and social groups. Experience has shown that it is usually sufficient to survey between twenty and thirty families in a group. As far as possible the families should be chosen by random selection, and every effort should be made to get a representative sample. Success depends on the tact and social skill of the organisers and investigators. Some housewives will never co-operate, but with care it should be possible to get the goodwill and help of at least four out of five.

TABLE 50, 9. *Scale of man values for caloric needs recommended by the League of Nations Health Organisation* (1936*b*)

Age	Male	Both sexes	Female
Over 60 . . .	...	0·8	...
14 to 59 . . .	1·0	...	0·8
12 and 13 . .	...	0·8	...
10 and 11 . .	...	0·7	...
8 and 9 . .	...	0·6	...
6 and 7 . .	...	0·5	...
4 and 5 . .	...	0·4	...
2 and 3 . .	...	0·3	...
0 to 2 . . .	...	0·2	...

A survey lasting less than seven days is of little value. In most countries families change their daily dietary habits at the week-end. To prolong a survey more than a week is irksome to the housewife and if necessary it is better to obtain more records from different families. In some countries there are marked seasonal variations in food intake and hence it may be necessary to repeat surveys at different times of the year. This is less necessary in towns than in country districts, for in the former the diet often changes surprisingly little throughout the year.

There are two major sources of error in a family survey. The housewife may, through ignorance or carelessness, fail to record or report all her purchases. Alternatively the housewife may ‘ put on a show ’ for the survey and feed her family better than normally. With good investigators the second error is the more probable and so surveys tend to overestimate normal consumption. A skilful investigator can often check up on these points and the record of any unreliable housewife should be discarded.

A valuable adjunct to a family dietary survey is often provided by an enquiry into the housewife's budget and the amount of money that she has available to spend on food. A comparison between this and local food prices serves as a check on the dietary assessment and sometimes provides clear evidence that the family concerned cannot possibly afford to purchase an adequate diet.

When properly carried out, a family dietary survey records with satisfactory accuracy the food intake of families and so provides a useful measure of nutritional status. Institutional surveys can be carried out on similar lines and are usually relatively easy.

An inherent drawback to family surveys is that no information is provided about how the food is distributed within the family. It does not distinguish between the food consumed by the housewife, the breadwinner, the children and other dependants.

Individual surveys.—The principle is the same as that of family surveys. The selected individuals, assisted and supervised by trained investigators, weigh and measure everything consumed at each meal. This is a much more exacting task than a family survey, for a great deal of co-operation and a modest degree of intelligence on the part of the subject is needed. Nevertheless, many excellent individual surveys have been undertaken. Children of different age groups, old people, miners, soldiers, housewives and people in various occupations have been studied. A properly conducted series of individual dietary surveys gives a good assessment of nutritional status.

CONCLUSION

So varied and numerous are the factors determining the health of a community that it is not surprising that single measurements of any one type have proved of little value *alone* in assessing nutritional status quantitatively. However, by a judicious application of a selection of the methods discussed in this chapter over a period of time, it should be possible to state with confidence whether the nutritional status of a community is changing—either for better or for worse. Such methods provide a practical means of assessing any government's food policy, provided that the investigations are carried out with due care and the results considered with a proper regard for the many difficulties involved in their interpretation.

CHAPTER 51

THE PREVENTION OF NUTRITIONAL DISORDERS

IN the practice of preventive medicine there are two main methods of attack upon any problem. The first is by means of education and the second, if necessary, is by legislation. Modern preventive medicine has developed from the experience gained in the control of the major infectious diseases. Field and laboratory research provide knowledge of the causation of a disease ; then, if that knowledge can be spread through all sections of the exposed population, the first and most important step in the control of the disease has been taken. However, education alone is seldom entirely effective in eradicating a disease and some legislation, which gives the government powers of compulsion, is usually necessary. Quarantine laws were the first and most important examples of such legislation.

If it were possible to use the knowledge which is already available, all the nutritional diseases described in Part III of this book could be eradicated. But elementary knowledge of the outlines of good nutrition and of their application to family feeding is lacking in varying degrees in all the continents of the world. Ignorance is a potent cause of ill-health and no one seriously questions the value of health education in nutrition.

GOVERNMENT CONTROL

The legislative control both of the production and distribution of food is a subject which has been much disputed. Arguments are often based on emotion rather than on reason and scientific knowledge. Two statements would receive general approval in many parts of the world. First, in time of serious lack of food—and especially in a famine—governments have the responsibility both for the procurement and distribution of food. For this purpose legislation must be extensive and rigidly enforced. Secondly, in times of prosperity, a minimum of government control is desirable, because the ordinary processes of supply and demand will determine satisfactorily what foods are available and how they are best distributed.

In practice, of course, neither famine nor real prosperity are usual. In most countries the supply and distribution of food is seldom entirely satisfactory and in many it is usually far from good. Some form of national or international food policy involving legislation and government control is desirable. But how much ? Here is the difficult question. It is essentially political in the true sense of that word. Broadly speaking those on the left, with their proper respect for the health and welfare of the poor and underprivileged, usually advocate more governmental control. Those on the right, with insight into the adverse effects of excessive regulations on enterprise—both in agriculture and trade—are for less. In fact, however, compromise is possible. In Great Britain, despite changes of government, a reasonably constant food policy has been followed for many years. Responsible people in all political parties have been in general agreement about the principles on which our food policies have been based. Condemnation has come only from extremists.

INTERNATIONAL ORGANISATIONS

The world's food supply is essentially an international problem and it is therefore proper to consider first the work which the various United Nations (UN) agencies are doing in attempts to improve nutritional levels in many countries of the world.

Farmers throughout the world will have to grow more food if the increasing population is to be saved from starvation. To achieve this, an extended practice of modern agricultural techniques, careful conservation of existing soils, great developments in irrigation and in the control and use of flood waters are necessary. Such projects are both difficult and expensive (Plate XXIII). To exploit the world's agricultural potentials there is a great need for financial capital and technical knowledge, in both of which many communities are deficient. Many undeveloped areas can only be made fully productive, within a reasonable period of time, if the indigenous people receive help in the form of both monetary loans and expert scientific advice from the richer communities. Such help requires co-ordination on a large scale, often on a world basis.

Financial investments in agriculture made with the *sole* purpose of yielding dividends are not likely to prove profitable to the human race as a whole. In the past, the purely financial motivation of farming has often led to a familiar picture of starvation and famine in one part of the globe coincident with the burning of surplus crops in another. In both instances poverty is the lot of the peasant farmer. The dividends that may arise from future large investments in agriculture cannot be counted in either dollars or sterling, but rather in a general improvement in human prosperity and health and the spread of peace.

This may sound trite and platitudinous. Yet the obvious—if true—may bear repetition and such views only received general international recognition when the UN Conference on Food and Agriculture was convened at Hot Springs, U.S.A., in May 1943. Forty-four nations were invited to send representatives to this conference, which was due to the initiative of President Roosevelt. Delegates reached agreement on a number of basic points, which later became foundation stones of the UN Food and Agricultural Organisation (FAO) policy. Some of these were :—

" The world has never had enough to eat. At least two-thirds of its people are ill-nourished in spite of the fact that two-thirds of the world's people are farmers.*

"The modern science of production shows that it is entirely possible to produce enough of the right kinds of foods.

"The modern science of nutrition proves beyond doubt that if all people could get enough of the right kinds of foods, the average level of health and well-being could be raised much higher than it is now.

"But production alone is not enough. Foods must be so distributed that the levels of consumption of those who do not have enough are progressively raised.

"This implies an expanding world economy, in which each nation will play its own part, but all will act together."

THE UNITED NATIONS FOOD AND AGRICULTURE ORGANISATION (FAO)

Out of the Hot Springs Conference, FAO arose and was formally founded at Quebec in October 1945. Forty-two governments ratified the original Covenant, and many more have since joined. In its conception and initial organisation FAO owed much to its first director, Lord Boyd Orr, who brought to his office the traditions of an Aberdeen farmer and the experience of a lifetime of work in medical and agricultural research, these being mixed and leavened by a spirit and eloquence characteristic of an ancient Hebrew prophet.

According to Article I of the FAO Constitution :—

"1. The organisation shall collect, analyse, interpret, and disseminate information relating to nutrition, food and agriculture.

"2. The organisation shall promote and, where appropriate, shall recommend national and international action with respect to—

- (*a*) scientific, technological, social and economic research relating to nutrition, food and agriculture ;
- (*b*) the improvement of education and administration relating to nutrition, food and agriculture, and the spread of public knowledge of nutritional and agricultural science and practice ;
- (*c*) the conservation of natural resources and the adoption of improved methods of agricultural production ;
- (*d*) the improvement of the processing, marketing, and distribution of food and agricultural products ;
- (*e*) the adoption of policies for the provision of adequate agricultural credit, national and international ;
- (*f*) the adoption of international policies with respect to agricultural commodity arrangements.

"3. It shall also be the function of the organisation—

- (*a*) to furnish such technical assistance as governments may request ;
- (*b*) to organise, in co-operation with the governments concerned, such missions as may be needed to assist them to fulfil the obligations arising from their acceptance of the recommendations of the United Nations Conference on Food and Agriculture ; and
- (*c*) generally to take all necessary and appropriate action to implement the purposes of the organisation as set forth in the Preamble."

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* This is certainly an overestimation in 1962 and may also have been in 1943. A modern critical assessment (Sukhatme, 1961) puts the number of malnourished people in the world as about 10 per cent. of the population. Even with this reduced estimate the number of people not getting enough to eat is about 300 million.

In the early days of FAO many people, including the Director-General, Lord Boyd Orr, hoped that the organisation would become an effective executive agency ; they wanted FAO to acquire the surplus food from the crops of the richer agricultural countries and to distribute these, as need arose, amongst countries afflicted with grave food deficiencies or famine. However, under its original constitution such power was not given. FAO could not order the adoption of particular policies nor embark on " the executive functions of purchase and procurement in order to stimulate output and equalise distribution." It could only recommend, demonstrate and discuss. This FAO has proceeded to do with vigour and intelligence. It has now settled down and assumed the function of a large-scale scholastic agency dealing in technical education. Since education is a slow process, to expect startling results too soon is wrong.

FAO, in co-operation with the UN Technical Assistance Board, is responsible for the selection and payment of the consultants and experts whose advice is required by member governments of the organisation. Fellowships are granted with the object of raising technological standards throughout the world. Experts have advised in such diverse fields as the improvement of hide and skin processing in Libya, irrigation in East Pakistan, fisheries development in Chile and improvement of water supplies in Syria. Examples of FAO fellowships are : to an Israeli for the study of milk hygiene in Denmark and Sweden ; to a Nepali to study dairying and animal husbandry in New Zealand ; to a Yugoslav to study home economics in Holland and France ; to an Egyptian to study rice production in Japan ; and to two Thais to study agricultural economics in the U.S.A. These are only a few examples of a large body of carefully selected people, who have been assisted in distributing technological knowledge throughout the world. They are certainly making a valuable contribution to material prosperity in many underdeveloped countries.

The series of Nutritional Studies published by the FAO Nutrition Division includes the following titles :—

Rice and Rice Diets.
Food Composition Tables.
Dietary Surveys.
Calorie Requirements.
Teaching Better Nutrition.
Kwashiorkor in Africa.
Maize and Maize Diets.
School Feeding.
Protein Requirements.
Calcium Requirements.

Each of these is a comprehensive review, which could only be undertaken by an international organisation. The series is a notable contribution to nutritional science.

In 1960 the position changed. Then the UN General Assembly requested the Secretary-General and the Director-General of FAO to report upon means whereby the best possible use could be made of surplus foodstuffs against hunger in food-deficient areas. They were asked to study methods whereby distribution of food surpluses could help the less-developed countries without slowing down their agricultural and economic development. This means that FAO can now, as part of its regular programme and through its Freedom from Hunger Campaign, help to co-ordinate arrangements between donor and recipient countries. It is hoped that FAO will now play a major part in the distribution of surplus foodstuffs. The principles involved and the United Nations action which resulted in these arrangements have been described by FAO (1963).

WORLD HEALTH ORGANIZATION (WHO)

WHO has its headquarters in Geneva with world-wide regional offices. Its nutrition section, which includes a research branch, works in close association with the nutrition division of FAO. Many field projects are planned in concert by the two organisations. A joint FAO/WHO expert committee on nutrition helps to guide their policies. WHO's most important nutritional work is carried out through the maternal and child health services which it has helped to establish in underdeveloped countries. In all underdeveloped countries mothers and young children are a group of the population particularly prone to nutritional disorders. The emphasis of WHO on the study of social anthropology and the necessity of understanding local customs and attitudes to food, particularly as applied to the welfare of mothers and children, is an important development in practical nutritional science.

WHO and FAO are organisations with essentially technical policies involving development and education. They do not dispose of funds to provide material aid to needy countries ; nor have they the means to provide relief on a large scale in an international emergency. UNRRA was an example of an organisation which was created in 1943 to help relieve the devastation caused by the world war.

United Nations Relief and Rehabilitation Administration (UNRRA)

When the tide of the Second World War began to turn against the Axis Powers, plans for bringing immediate relief to the invaded countries awaiting liberation were pursued with vigour and imagination by the United Nations. As early as November 1943 representatives of forty-four nations met in the White House, Washington, at the invitation of President Roosevelt. There they brought into being—UNRRA : a unique organisation for international relief on the grand scale. The countries that had not been invaded agreed to contribute 2 per cent. of their annual income to the resources of UNRRA. The largest contributions were from the U.S.A.—£675 million ; Great Britain—£155 million and Canada, £35 million. With these vast resources—three times more than was spent on relief after the first world war—UNRRA poured vital supplies into Albania, Austria, Byelorussia, China, Czechoslovakia, Italy, Greece, Poland, the Ukraine and Yugoslavia. Limited aid was also given to seven other countries. In the first three years of its operation, beginning in March 1945, 25 million tons of goods costing £750 million were shipped overseas by UNRRA in more than 6000 ships. Other goods were purchased on the spot from Army supplies and other sources and used for relief purposes. This huge volume of essential goods included locomotives, trucks and freight cars necessary for the transport of food to centres of populations, more than 300,000 farm animals, thousands of tractors and ploughs and many tons of seed grains necessary for restarting agriculture in devastated areas ; in addition UNRRA provided fully equipped hospitals, and much-needed medical supplies and personnel, necessary for the health and life of the invaded countries. But agriculture could not be set on its feet overnight and, in the meantime, the people had to be fed ; the most vital part of UNRRA's work was therefore the provision of food ; the foodstuffs were of every kind including hundreds of tons of dried milk for children, and vast quantities of cereals. In all, UNRRA shipped enough grain to make about 12,000 million 1 lb. loaves, enough to give five such loaves to every man, woman and child in the world. The result was that at least three famines, that might have involved 15 million people in Europe, were prevented ; untold misery, hardship and underfeeding among many more millions were alleviated.

It was a condition of UNRRA aid that the supplies sent in should be distributed without regard to politics, race or religion. It is a pleasure to recall that these conditions were effectively observed.

United Nations International Children's Emergency Fund (UNICEF)

When the work of UNRRA ended, many countries still needed assistance with health problems arising out of the war. Pressing problems of child-health and child-welfare still remained. To help solve these, UNICEF was formed and began to operate in the winter of 1947. The Fund has aided governments to provide every type of essential need for children. Food, footwear, diapers, medicines, trained children's workers, etc., all have been made available to the needy without discrimination of race, creed, nationality or political belief. Help has been given in many parts of the world. At first the greater portion of the financial resources of the Fund, which amounted to over $100 million was devoted to the provision of children's meals. For long periods, some 4 million children were receiving each day a meal partly provided by UNICEF. The continuing nature of these problems and the effective way in which UNICEF organised the provision of material aid of every sort to needy children and their mothers led the UN to establish it on a more permanent basis. UNICEF remains a non-technical organisation and works in conjunction with FAO, WHO and other UN agencies, including the Bureau of Social Affairs and the Educational, Scientific and Cultural Organisation (UNESCO). Many joint projects for the control of diseases such as malaria, tuberculosis and yaws have been successfully carried out. Training and education in nutrition, agricultural extension and home economics are organised in an ever-increasing number of countries. UNICEF continues to undertake the purchase and free distribution of milk powder to needy children and mothers throughout the world, and now co-operates with FAO in the development of milk-processing plants and dairies in countries which have available sources of fluid milk. Any UNICEF contribution to a country was, and still is, matched in value by the government of the assisted country from resources which are available locally.

In addition to its regular programme UNICEF provides material aid, including food, medical equipment and supplies, blankets and other essential items, to countries overtaken by natural disasters, such as flood, earthquake or famine. Such necessities are also supplied for the use of political refugees in camps supervised by the United Nations. Under such conditions WHO and FAO provide professional men and women to help countries re-establish their public health and agricultural services. Recent examples of catastrophes where the victims have been much helped by joint action on the part of UN agencies are, the earthquakes in Chile in 1960, the hurricane which caused much damage in British Honduras and the floods which resulted in famine in Somalia, both in 1961.

UNITED NATIONS SPECIAL FUND

The Special Fund was formed in 1959 primarily to assist countries in the development of industry of all sorts, including the training of technologists and technicians. At the request of governments and in conjunction with FAO, projects are being developed in many countries which will help to improve the state of nutrition of the people, such as large-scale irrigation schemes and the formation of institutes of food science and technology.

THE COLOMBO PLAN

In January 1950, Commonwealth Foreign Ministers met at Colombo to exchange views on world problems and in particular on the needs for development of South and South-East Asia. Out of this meeting the ‘Colombo Plan’ developed (Commonwealth Consultative Committee, 1950). It is essentially a scheme for facilitating the introduction of Western scientific techniques into Asia and in particular for providing the finance necessary for material equipment and the education of the technicians. From the beginning, developments have been considered under four main heads: (1) agriculture and irrigation, (2) transport and communications, (3) industry, fuel and power, (4) health, education and housing. Subsequently all the countries in the area outside the Commonwealth have joined and in addition, the U.S.A. and Japan.

The bulk of the capital to be spent on development must be raised within the countries themselves. India's Third Five Year Plan, which aims at an increase in national income of 5 to 6 per cent. per year, with emphasis on the development of agriculture to achieve self-sufficiency in food grains and meet the requirements of industry and exports, envisages the investment of Rs.102,000 million (about £7,670 million) from public and private sources. The value of aid in 1959-60 from donor countries to the Colombo Plan countries was approximately £625 million, and total aid since the beginning of the Colombo Plan has exceeded £2,850 million. The International Bank for Reconstruction and Development has made loans of £340 million. The Commonwealth Consultative Committee which meets annually reported (1960) that the population of South and South-East Asia is now increasing at an annual rate of approximately 2 per cent. The increase in national income in most countries of the area, which ranges from about 3 to 5 per cent. per year, has to meet the larger food requirements and other essentials of the growing population as well as improved standards of living and capital formation.

In the area as a whole there has been a substantial increase in food production since the inception of the Plan, attributable to the use of better varieties of seed, improved irrigation and pest control, and increased and better use of fertilisers.

Technical assistance has played an important role in the development of the area. Since 1950 training has been given to over 23,000 agriculturists, water engineers, medical men, food technologists and many others, and the services of nearly 11,600 experts have been provided to countries in the area by members of the Colombo Plan and by agencies of the United Nations.

The first report on the Colombo plan written in 1950 ended with the words : " In a world racked by schism and confusion it is doubtful whether free men can long afford to leave undeveloped and imprisoned in poverty the human resources of the countries of South and South-East Asia, which could help so greatly not only to restore the world's prosperity but also to redress its confusion and enrich the lives of all men everywhere."

Subsequent annual reports have been essentially economic documents and they make dry reading. The economists who write them do not help us to visualise the new crops, the hydro-electric plants and the new hospitals and schools that are growing up. The Colombo Plan has been an instrument which has made possible great achievements, but much more remains to be done before the people of South and South-East Asia reap in full the benefits of scientific discoveries.

FOOD SUBSIDIES

The importance of poverty in preventing the equitable distribution of foods has already been stressed. The question of the prevention of poverty is beyond the scope of this book, but the discussion of methods for relieving one of the major effects of poverty, namely malnutrition, is relevant. Food subsidies have this object. During the Second World War the British Government lowered and controlled the prices of beef, mutton, bacon, bread, sugar, milk, potatoes, margarine, butter, cheese and eggs by means of subsidies. These varied from 20 to 50 per cent. of the true cost of the food. In 1947 the annual cost of these subsidies was £500 million and the Chancellor of the Exchequer estimated that the average family of four received an equivalent of 12s. a week in food subsidies.

Subsequently these subsidies on consumer goods were reduced and by 1954 all had gone except that on Welfare milk. There are still large subsidies to agriculture ; for the year ending 31st March 1960 the total cost of exchequer support to agriculture was £223 million which included £84 million for farming grants and subsidies and £138 million for the implementation of agriculture price guarantees. It is impossible to state how much of this lowers directly the price of food. Nevertheless the British housewife does not pay the full economic prices for all the food she buys. Without these agricultural subsidies, the cost of living would be higher.

RATIONING SCHEMES

Rationing is simple in principle and applicable to all foods which are available only in limited supplies, and which, on either physiological or psychological grounds, have been considered essential for the health of the people. Thus during the Second World War, in Great Britain, a country in which much of the food eaten is imported from overseas, it was considered necessary to ration the following foods : butcher's meat, bacon, milk, cheese, sugar, fats, and in addition during 1946-48 bread and in 1947-48 potatoes. All forms of rationing were removed by 1953. Elaborate controls are only possible when the people have the necessary discipline and administrative aptitude. In countries with a simpler dietary pattern and a limited administrative machinery, it is both unnecessary and impractical to attempt so much. For instance, during threats of famine in post-war India, it has been usual to ration only the staple grain of the district. This has proved for the most part to be practical, that is within the scope of the administration, and yet effective in preventing serious deterioration of health in threatened areas. By contrast after the war, in the British and U.S. Zones of Germany, elaborate schemes for rationing of bread, cereal products, potatoes, fats, sugar, meat, cheese, milk, fish and dried fruits were drawn up and put into operation. Much confusion was caused by the inability of the German authorities to enforce these regulations. In consequence large black markets thrived. When advising on rationing needs, medical opinion must always consider the normal dietary habits of the population, their probable reaction to discipline and the efficiency of the machinery of administration. Ineffective control is usually more demoralising than no control.

In order to make rationing more elastic and to meet to some extent individual variations in taste, a ' points ' system was introduced in Great Britain during the Second World War. This regulated the consumption of a large variety of foods which custom had long made part of our national diet, and of other foods which were scarce or in limited supply. Foods ' on points ' were for the most part not strictly essential to meet physiological requirements, but were needed to maintain a varied and attractive diet. Psychologically the ' pointed ' foods were very important ; they included oatmeal, biscuits, flour, tinned and dried fruits, tinned meat and vegetables, various sweets and preserves. Each person could use his or her points as desired, and this allowed an important element of variety and choice in an otherwise rigid system. The value in points of any food could be altered according to variations in the supply. It was accordingly an elastic system of control.

Black markets.—No account of rationing systems would be complete without a reference to the ' black market.' Any system of rationing will fail if a large proportion of goods supposed to be rationed reaches the consumer by channels independent of government control. Such distribution of rationed goods through illegal channels is known throughout the world as a ' black market.' The size of black markets is a measure of the efficiency of the administration and the extent to which the government represents the will of the people. Human nature necessitates that in time of scarcity some exchange of primary products and services must occur without the use of the medium of money and outside any state control. Experience has shown that, as long as this barter of services and products is limited to exchanges between principals for their personal use, it has little effect on the efficient working of a rationing system. No government can hope to prevent such exchanges. They were common in both Scotland and England throughout the war, and yet did not seriously affect the distribution of rationed goods. Once, however, such exchanges become organised by intermediaries, who themselves produce no goods and perform no essential services, then chaos results. There is a class of men, the black marketeers, who if the government is weak and shortages are severe, are prepared to exploit the difficulties of others for their personal gain. The control of the activities of such men is a most important task. Bengal and Germany in recent years have known the evils that result from black marketeers. Such offenders against food regulations should receive the severest penalties of the law.

WELFARE FOODS

Experiments on animals have indicated that the processes of growth in children and of reproduction in women require exceptional amounts of certain nutrients. The growing animal or child needs protein, calcium and iron, and vitamins A and D in larger proportion than does the adult. In times of war or agricultural and economic depression, experience has shown that signs of malnutrition can usually be most readily demonstrated in children and reproductive women. Both the infant and maternal death-rates may reflect deficiencies in the diet. Children and expectant nursing women have been said to constitute a 'vulnerable group,' particularly prone to develop nutritional disorders. Where there are large numbers of old people, these form another vulnerable group. In many countries charitable organisations and both central and local governments have developed ways and means of protecting vulnerable groups in times of scarcity and hardship.

Since time immemorial religious people have felt themselves under obligation to help to feed the children of the poor. Such help has usually been sporadic and not always well directed to physiological needs. Historically the experiments carried out by Auden (1923) in Birmingham and by Corry Mann (1926) were of great importance in showing that even a comparatively good diet might not supply all the *specific* needs of growing children. Corry Mann carried out controlled experiments on groups of boys in institutions near London. The basic diet of the boys was generally considered to be satisfactory at the time, though we now know that the diet was far from ideal ; yet it was not grossly deficient in any factor and there was no evidence of any nutritional disorders amongst the boys. Corry Mann showed that when a group of these boys aged 7 to 11 years were given a supplementary ration of a pint (600 ml.) of milk a day these boys grew 0·8 in. taller and 3·13 lb. heavier in a year than a similar group living side by side with them, but receiving no supplement. Further, he showed that supplements of sugar, butter, water-cress and other foods did not produce the same beneficial effects as supplements of milk. In the opinion of the schoolmasters the milk improved the general alertness and vitality of the children. Similar experiments have now been carried out in many parts of the world on children of all ages and the beneficial effect of extra milk on children's health has been frequently demonstrated under a variety of circumstances. Such demonstrations have been and no doubt will continue to be most useful educationally—especially in underdeveloped countries—in that they draw the attention of health authorities and the public to the special needs of children.

One important discordant result has been obtained by Widdowson and McCance (1954). They found that there was no increase in the growth rate or general health of German children aged 5 to 14 years who received a supplement of 500 ml. milk daily for 6 months in 1948. The basic diet of the children contained ample quantities of bread (85 per cent. extraction flour), liberal amounts of vegetables, but very little of milk or meat or indeed of any food of animal origin. On such a diet milk would have been expected to increase growth and well-being. Another instance of the failure of protein-rich dietary supplements to enhance the growth rates of children has been reported from Nigeria by Nicol and Philips (1961). A group of secondary boarding school boys ate 50 g. of groundnut flour daily as an addition to the school diet ; a control group, matched for age, weight and height, received a starchy supplement and tablets providing calories, minerals and vitamins in amounts similar to the groundnut flour, but only traces of protein. After 9 months no significant difference in the heights or weights of the two groups, each composed of 50 boys, was found. Like the German rations described by Widdowson and McCance (1954), the regular school diet contained good amounts of cereals, legumes and fresh green and red vegetables but little meat, fish or milk. Using the method advocated by the FAO Committee on Protein Requirements (p. 87) it was calculated that the school diet supplied the boys with slightly more than their ' minimal protein requirement ' : the diet supplemented by groundnut flour provided the full ' safe practical allowance ' of protein. These German and Nigerian trials suggest that increasing the intake of protein over a certain minimum level (the quality of the protein being considered as well as its quantity) does not accelerate growth rate.

In 1940 when the food situation in Great Britain gave rise to grave anxiety, a complicated and extensive system of Welfare Foods was introduced to protect the vulnerable group of women and children, and supplementary rations were made available for the sick. In the next 5 years the health of children of all ages and of mothers improved markedly. Mortality rates were decreased and growth rates increased. This improvement occurred despite a marked decline in the standards of housing, and the hazards to health associated with the evacuation of large numbers of children and the disruption of families. There can be no doubt that the war-time Welfare Food Services were a notable contribution to child health, but such an elaborate scheme could only be carried out in a well-disciplined country with an exceptional aptitude for administration. During the war many other countries operated less ambitious schemes with considerable success.

Since the war with the general rise in prosperity and the greater availability of food, Welfare Food Services have been markedly curtailed. A joint sub-committee of the Central and Scottish Health Services Councils was set up in 1956 to advise on the Welfare Foods Service. Their report (1957) recommended the discontinuation of Welfare orange juice after the age of 2 years, as the more varied diet after this age was considered to provide sufficient ascorbic acid. They also recommended reductions in the vitamin D content of cod-liver oil, National Dried Milk and infant cereals to a level sufficient to prevent rickets, but low enough to avoid the risk of hypercalcæmia. Table 51, 1 shows the details of the allowances in 1958. The vitamin preparations are now distributed by local health authorities.

The use made of these Welfare Food Services is interesting. In 1960, 95 per cent. of those entitled to obtain milk or National Dried Milk under the scheme did so. However, only 8 per cent. of the cod-liver

TABLE 51, 1. *Welfare Foods allowances to children in* 1958

(1) ALLOWANCES OF MILK TO YOUNG CHILDREN

	Age	Quantity
(*a*) Fed on liquid milk . .	0–5 years	7 pints per week at reduced price
(*b*) Fed on National Dried Milk *	0–5 years	1 tin (20 oz.) per week equivalent to 7 pints liquid milk, plus the following additional amounts for a child under 1 year of age :— 0–10 weeks † . . 31 tins 11–17 weeks † . . 28 tins 18–21 weeks † . . 24 tins 22–25 weeks † . . 20 tins 26–29 weeks † . . 16 tins 30–33 weeks † . . 12 tins 34–40 weeks † . . 8 tins 41–44 weeks † . . 4 tins 45–48 weeks † . . 2 tins 49–52 weeks † . . 1 tin

(2) ALLOWANCES OF MILK TO HANDICAPPED CHILDREN

	Quantity (per week)	Certification required
Children over 5 and under 16 years of age who cannot attend school because of physical or mental handicap and who are thereby deprived of the benefit of school milk	7 pints of liquid milk at reduced price *or* 1 tin (20 oz.) National Dried Milk in lieu	F.W. 20 by parent and F.W. 21 by Local Education Authority

The above allowances are available on Welfare Milk Token Book (Child) (F.W. 1) and National Dried Milk Supplementary Token Book (F.W. 11).

(Ministry of Agriculture, Fisheries, and Food. *Some Notes on Nutrition Policy in the United Kingdom*), 1939-57.

* National Dried Milk is of two kinds : full-cream of 26 to 27 per cent. fat content, and partly skimmed, 16 to 17 per cent. fat content, in 20 oz. containers.

† Child's age at time of application for National Dried Milk tokens.

oil, 31 per cent. of the vitamin tablets and 39 per cent. of the orange juice to which people were entitled were taken up. Since June 1961 free issues of vitamin supplements have ceased. Supplies are obtainable at Welfare Clinics and Welfare Food Centres at the following costs :—

Concentrated orange juice, 1s. 6d. for a 6-oz. bottle.
Cod liver oil, 1s. for a 6-oz. bottle.
Vitamin A and D tablets, 6d. for a packet of 45.

These prices cover cost to the Government. Despite educational drives by Maternity and Child Health Services, consumption of these supplements has fallen markedly since these prices were introduced. It is extremely difficult to assess the value of these supplements in Great Britain to-day. We know of no clear-cut demonstration that any group of children, who do not take these supplements are in any way worse off than those who do. However, we cannot be certain that those children who take them—of whom many come from the poorer families—might not suffer if they did not. Rickets and scurvy are major disorders of childhood, which have caused much suffering in this country. Both are very uncommon to-day.

We have described in detail the Welfare Food Services in a well-organised country, both in times of relative prosperity and of hardship. The Services are essentially a function of central government. In underdeveloped countries, where the need for Welfare Foods for mothers and children is so great, central governments for the most part have neither the finances to obtain them nor the administrative machinery to distribute them. The distribution of Welfare Foods is usually a function of the Maternity and Child Health Services and can expand only as these are developed. This may often be a function of local rather than central governments.

The principles of the Welfare Food Services are the same in underdeveloped areas as elsewhere. The vulnerable groups need extra protein and extra vitamins. International organisations, such as UNICEF and many voluntary organisations, have been responsible for distributing large amounts of skimmed-milk powder—the surplus of the butter industry in North America, Australia and New Zealand—but this source of protein is only available in limited amounts. In some underdeveloped countries it is possible to increase the local production of milk and also facilities for processing it. FAO and UNICEF have helped governments greatly in these respects. In others, where pasture is extremely limited or the tsetse fly prohibits the existence of dairy herds, such an increase will be impossible to achieve for many years to come. It is now known that suitable mixtures of vegetable proteins can replace satisfactorily the animal protein in the diet of the young child. The production of suitable mixtures of vegetable proteins from plants which can be grown locally is essentially a problem of regional research. WHO, FAO and UNICEF have a joint programme for the biological evaluation, by clinical trials, of vegetable proteins and mixtures of protein-rich foods of vegetable origin ; they also help in the technology necessary for the production of such products, and in their introduction into the dietary patterns of the peoples living in such areas of the world. Soya products, groundnut flour, cottonseed flour and sesame flour, and mixtures of these foodstuffs with cereals have been proved to be very valuable foods. Extra vitamin D is seldom necessary in the tropics, but vitamin A supplements are often required for mothers and young children. Fish-liver oils are valuable sources of vitamin A activity and so is red palm oil ; these are being developed in many tropical countries. In rice-eating areas many children will benefit from a regular supplement rich in the B group of vitamins. The protein-rich flours mentioned in the preceding paragraph contain good amounts of these and dried yeasts and suitable rice-bran preparations can also fill this need. But the supply of both is in most

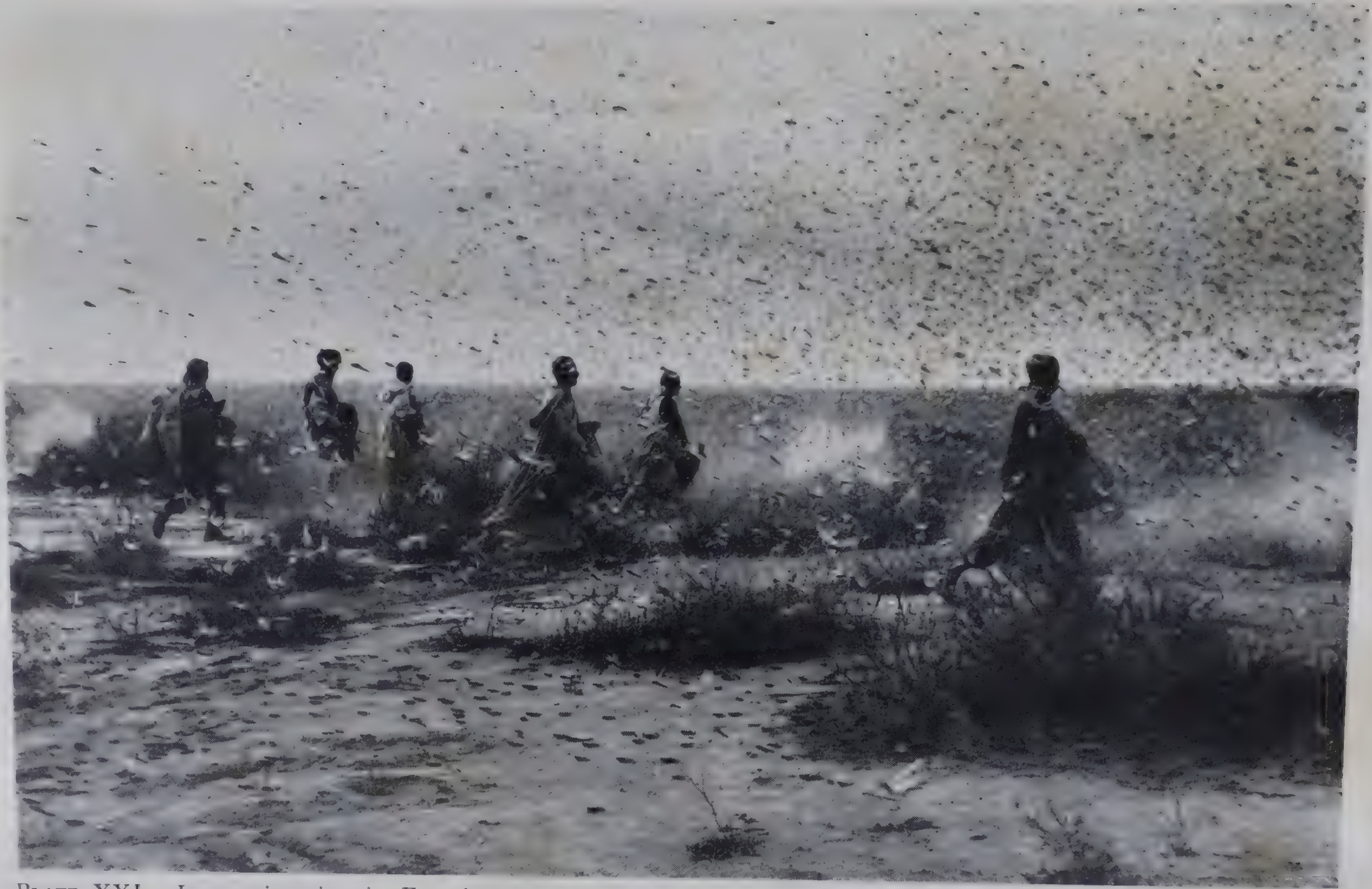

PLATE XXI. Locust invasion in French Morocco. Attacking an adult swarm with poison bait. (FAO photo by Studies du Souissi, Rabat.)

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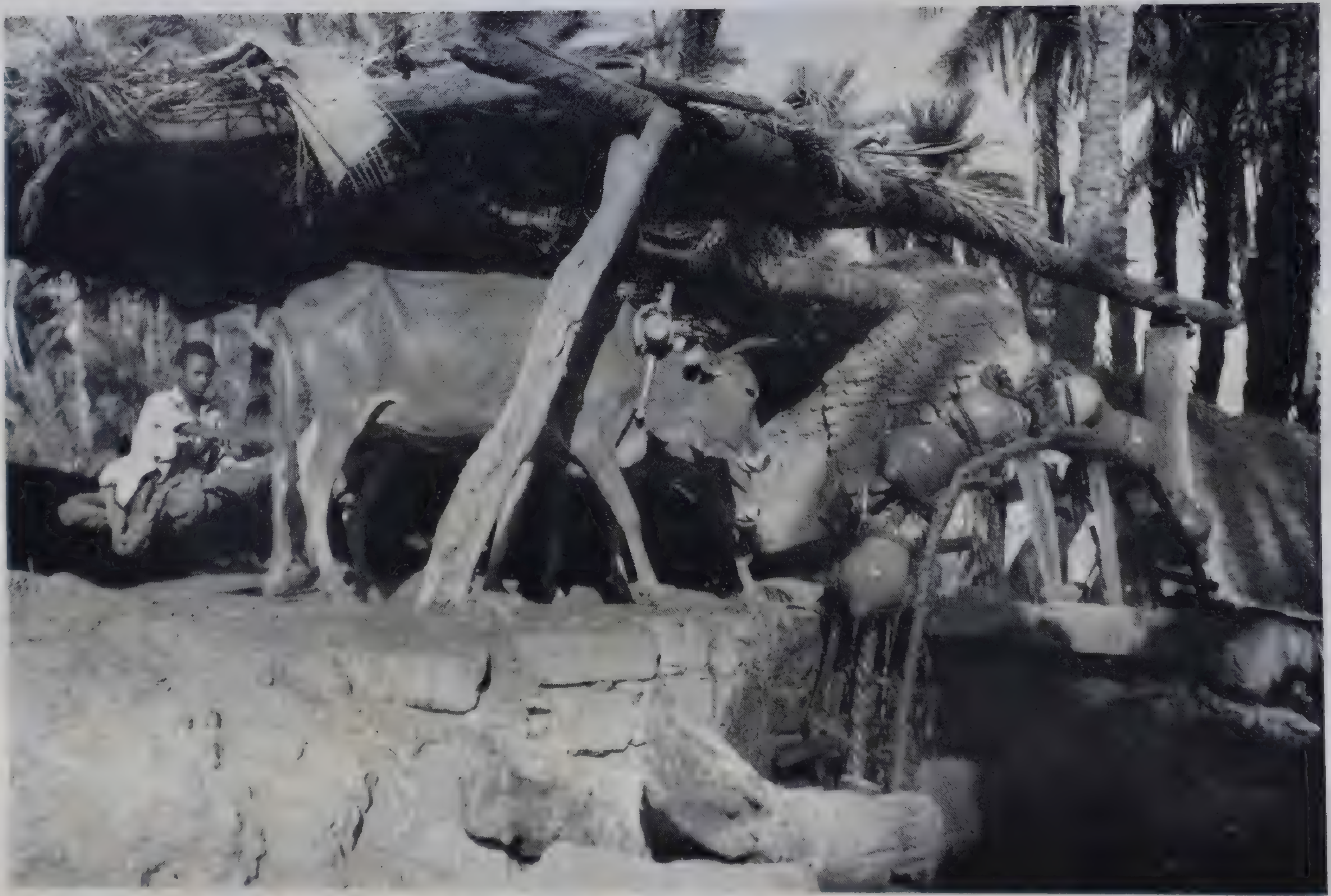

Plate XXII. Irrigation by sakia, one of the most ancient types of water wheels, can still be seen in many parts of the world. (FAO photo by P. Morin.)

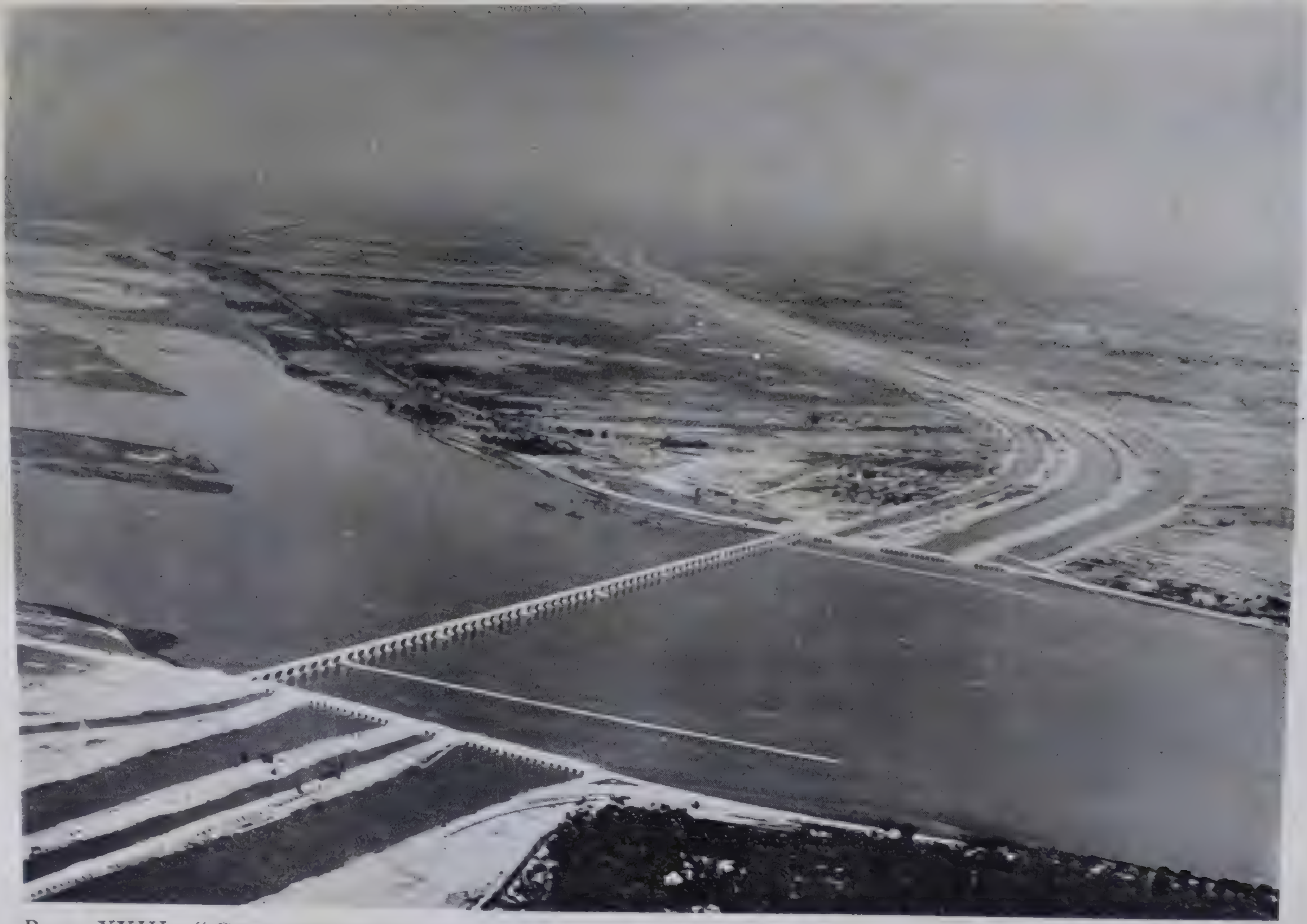

PLATE XXIII. "Great developments in irrigation and in the control and use of flood waters are necessary. Such projects are both difficult and expensive" (p. 724). The Lloyd Barrage and Lansdown Bridge on the River Indus, Sind, Pakistan.

PLATE XXIV. A. A school garden in Guatemala, where children help to produce vegetable crops, and incidentally learn that these add important nutrients to the diet. (FAO photo by Miss Jean Ritchie.) B. A refresher course for Public Health nurses in Burma with a demonstration of food values on the flannelboard. (FAO photo.)

A

B

Plate XXV. A, Children in Tokyo eating a school meal. School meals are part of the Japanese Government's nutrition programme. B, An FAO home economist in an Egyptian village showing fellahin women how to make up a formula for infant feeding. (FAO photos.)

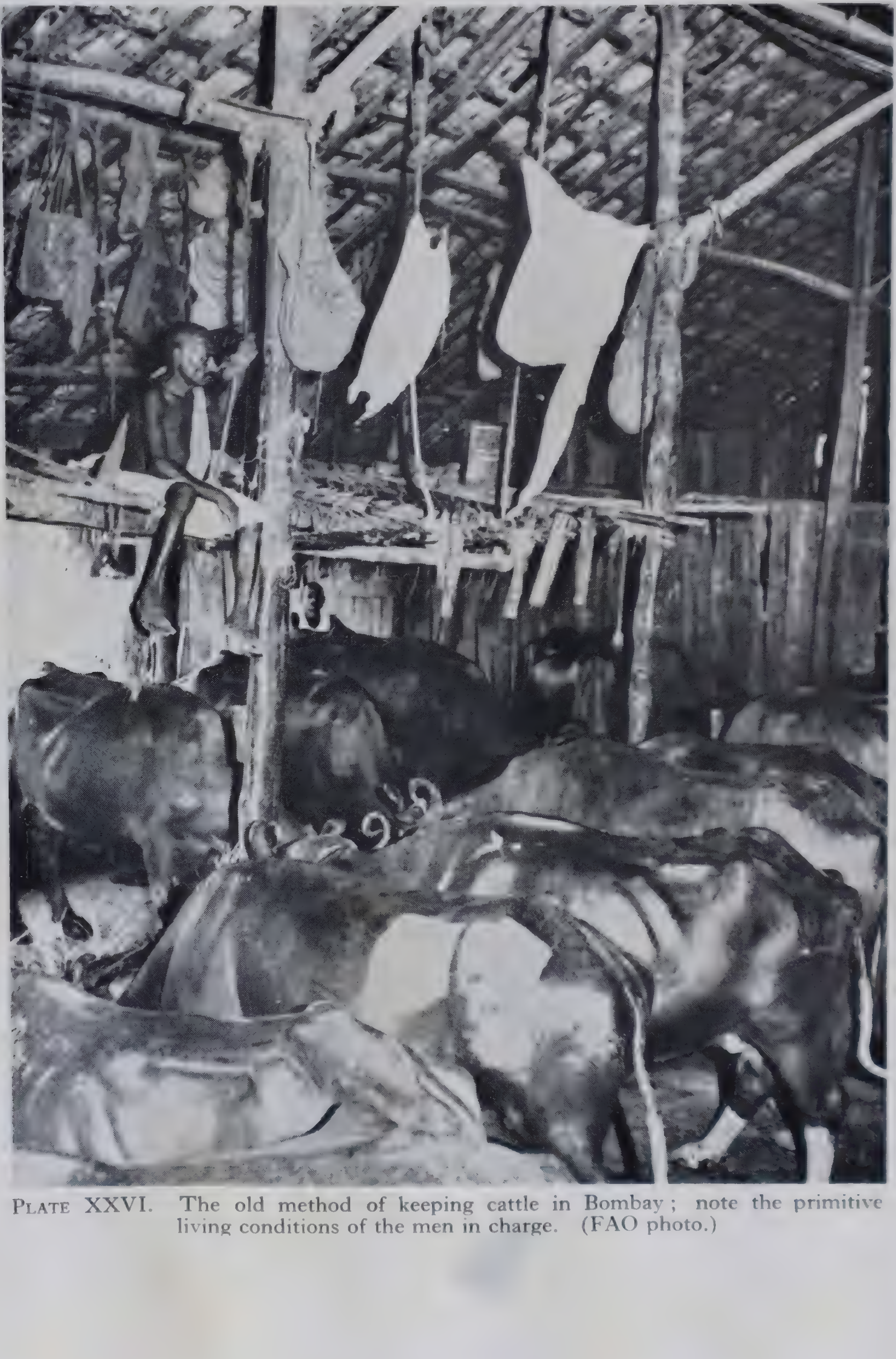

PLATE XXVI. The old method of keeping cattle in Bombay; note the primitive living conditions of the men in charge. (FAO photo.)

PLATE XXVII. Bombay. To improve the supply and quality of milk the Government began construction in 1948 of cowsheds and dairies on the outskirts of the city. FAO sent an expert in animal production to advise on a programme to improve cattle herds, and also a dairy technologist. To-day the colony consists of more than thirty self-contained farm units, each housing 500 head of cattle in modern hygienic conditions. (FAO photo.)

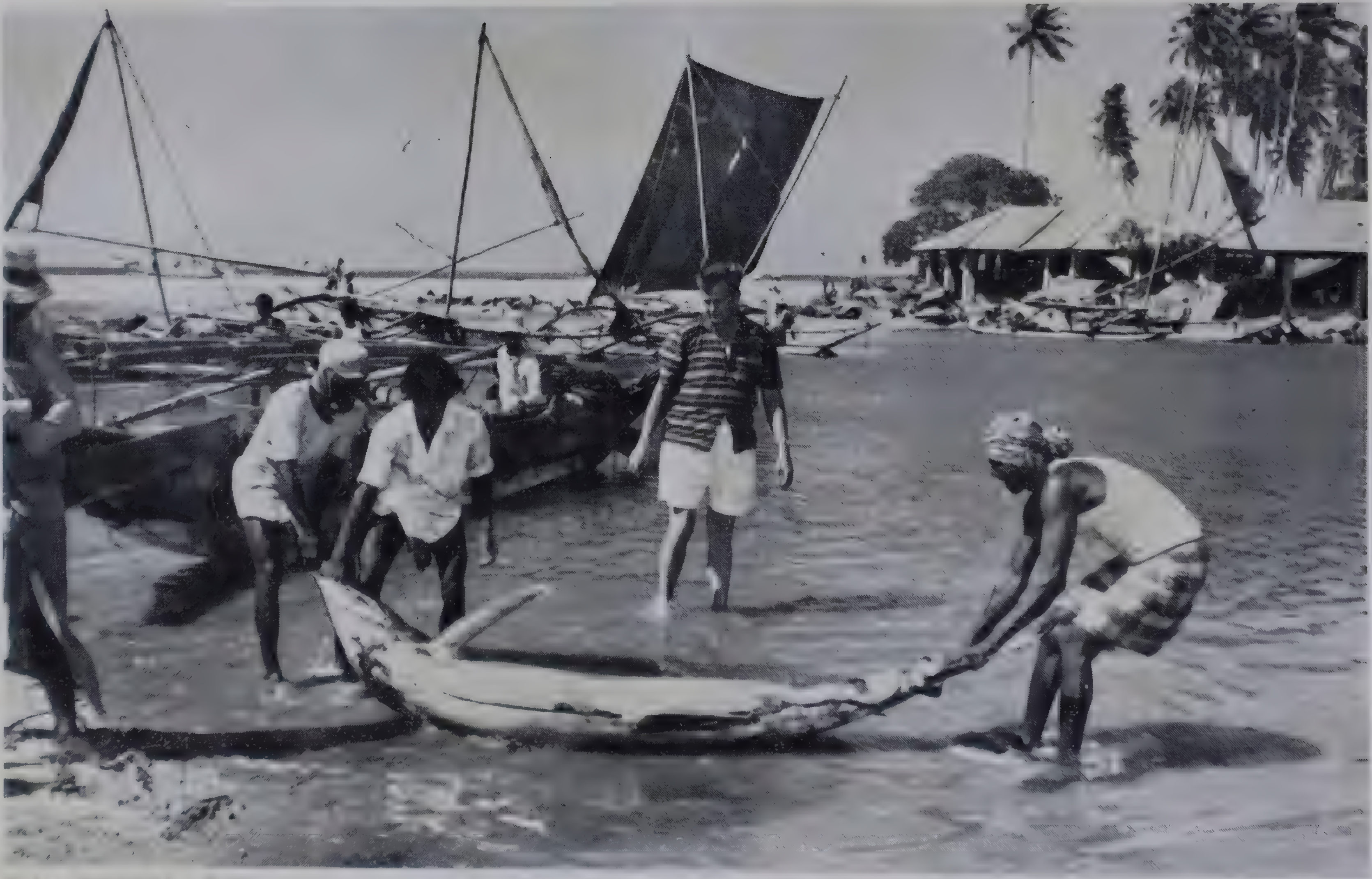

PLATE XXVIII. FAO marine engineer, Mr E. A. Kvaran (Iceland), watches the landing of a swordfish (or sailfish). Longline fishing for tuna, sailfish, etc., is becoming increasingly popular in Ceylon, particularly at Negombo, a major west coast fishing centre. Note the old boats and fishing gear. (FAO photo by S. Bunnag.)

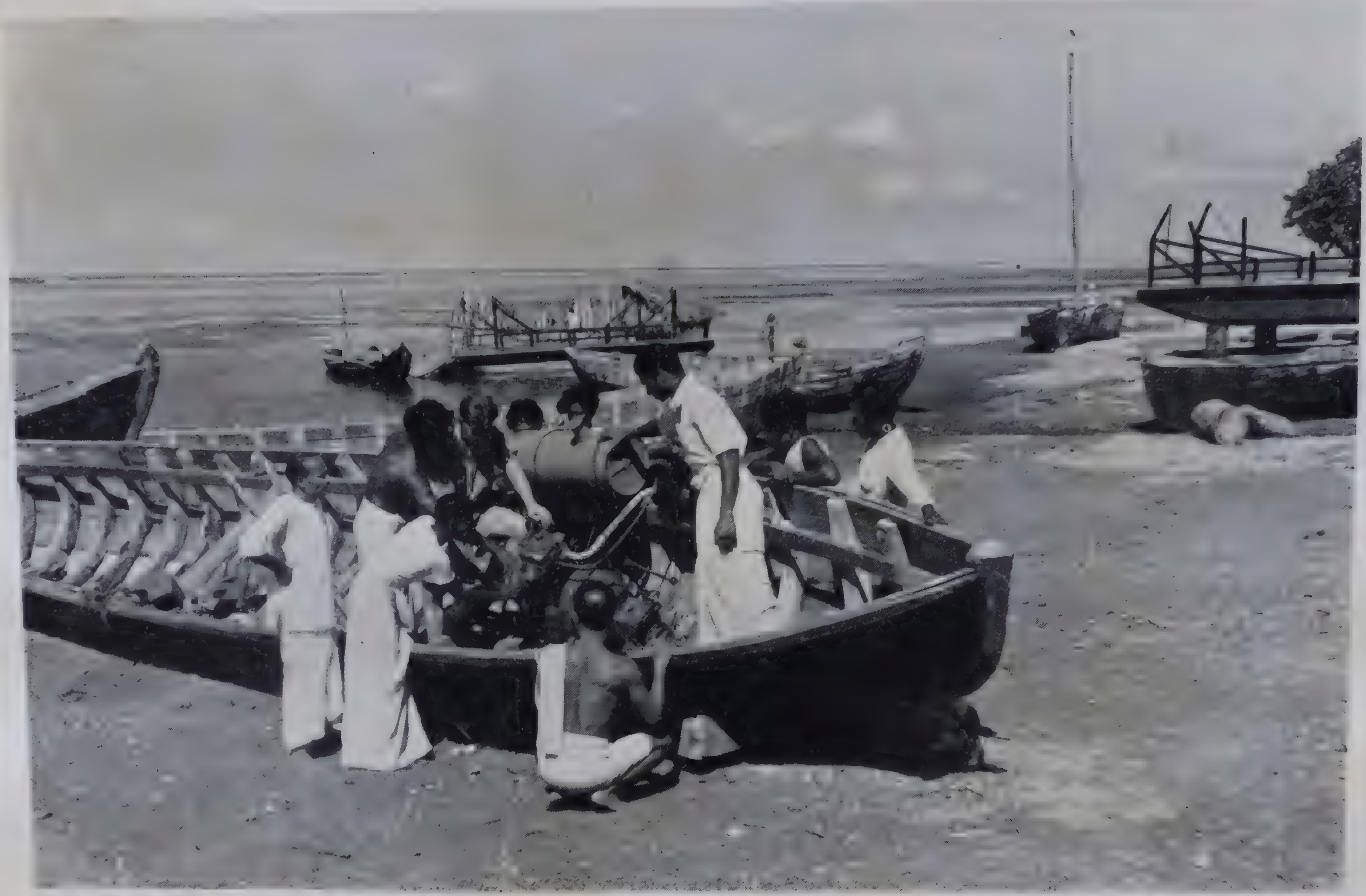

PLATE XXIX. FAO installed two engines on local fishing craft. This experiment proved successful and the Colombo Plan has since presented Ceylon with forty or more engines. (FAO photo by S. Bunnag.)

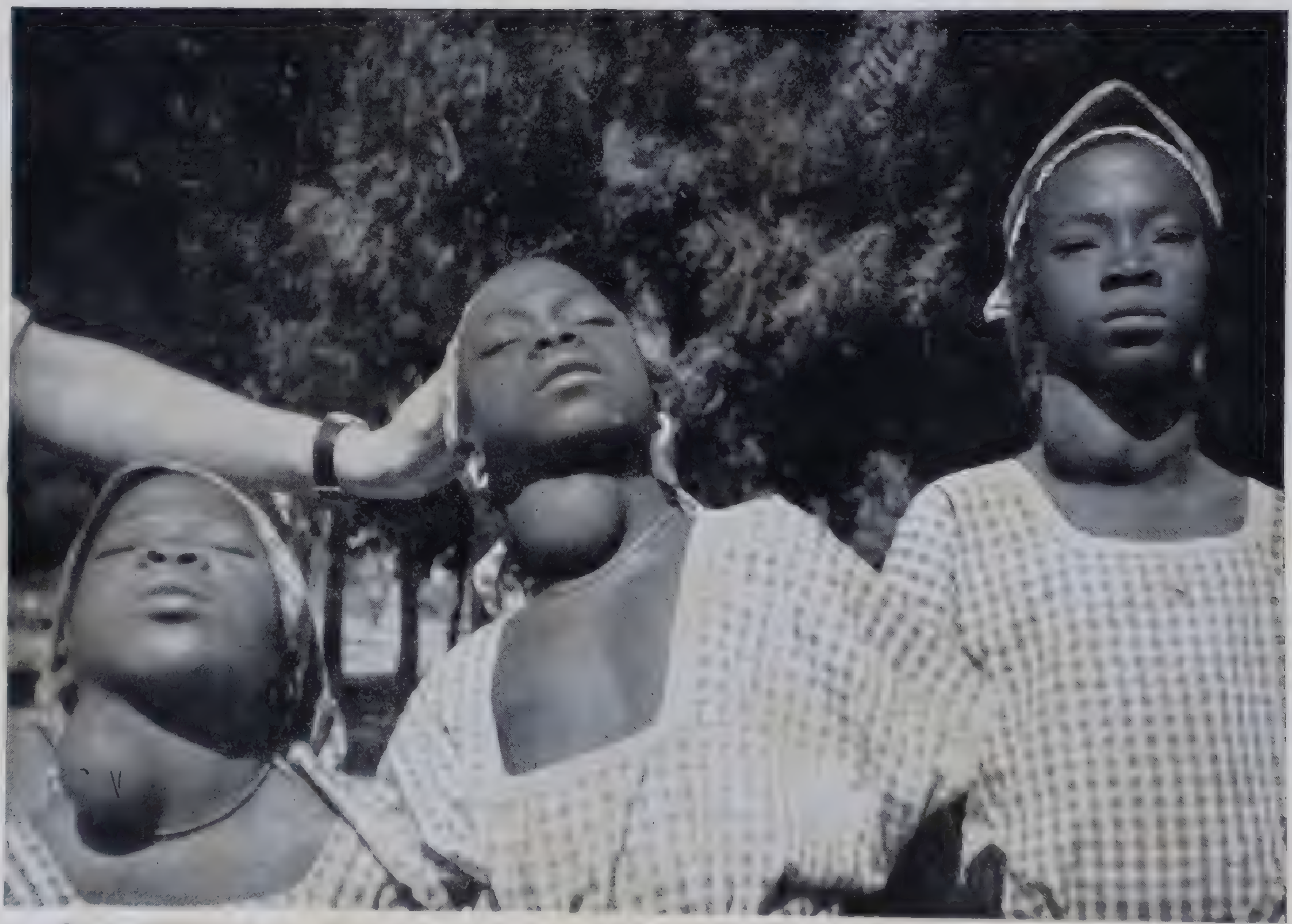

Plate XXX. Goitre in Nigerian girls. Reproduced from *British Journal of Nutrition* (1954), **8**, 99.
(Photograph by Professor R. W. B. Ellis.)

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districts insufficient for large-scale distribution. In many underdeveloped areas the supply of ascorbic acid is very variable and dependent on the fruit season. There is often a need for experiments in methods of preserving fruit and fruit juices.

In conclusion we should like to pay a tribute to the Gota de Leche organisations in South America. Many private individuals have given both of their time and their money to these organisations, which distribute milk to poor and needy children. One of us (R. P.) has had the opportunity to see the benefits to child health that can follow upon this work.

COMMUNAL FEEDING

School Meals

The provision of meals in schools is a measure designed to protect children against deficiency diseases and other effects of improper nutrition. There are few, if any, countries which do not have some school meal services although, on account of the high cost of running them, many are but little more than demonstrations. Great Britain has a large and comprehensive system of school meals which, like many of our apparently new social services, has its roots deep in history. As in most European countries, our present centralised services, which are almost entirely financed and operated by public money, have evolved out of small private charities. Thus in 1864 the Destitute Children's Dinner Society was founded and, 5 years later, had 58 dining-rooms open in London. Other charities, notably the London School Dinner Association, followed and spread to other big industrial cities. These societies at first only provided dinners in the winter. Elementary school teachers and others soon realised that the work of these charities was not sufficiently extensive to meet the needs of the great number of children in nineteenth-century Great Britain, who were unable to derive full benefit from their education on account of an insufficiency of food at home. The extent of malnutrition and subnutrition amongst the population, disclosed during the recruiting drives for the South African War, had disturbed the social conscience and prepared public opinion for an Act of Parliament in 1906, which gave local authorities permission to provide free meals for certain pupils from public funds. At first only destitute children received help, but the service gradually expanded (with many ups and downs) and by 1939 about a quarter of a million children were having midday meals of some sort provided away from home.

The outbreak of war in 1939 was a great stimulus to the scheme and, indeed, to a complete transformation of policy based on the following considerations. First, it was realised that growing children need food above the normal ration of the adult community and need especially foods rich in proteins, minerals and vitamins. Secondly, with the great increase in the employment of women in industry during the war, many mothers on account of their work were no longer able to spare the time to prepare adequately their children's meals. Bombing and the subsequent movements of population led to a great development of catering establishments outside the home, and children's needs were best met by school canteens. At the end of 1946, 2¼ million children in England and Wales were receiving school meals. There were then about 19,000 kitchens which served about 24,000 schools. About 15 per cent. of the children receiving the meals did so free of charge, the remainder paying a sum, which usually covered at least the cost of the food supplied. With the gradual change-over from war to conditions of peace this policy has not changed ; the present aim of the British Government is to provide a midday meal for every school child. In 1960, in England and Wales 3,400,000 school children were taking a midday meal at school—about 46 per cent. of the children attending. In Scotland the figure is 33 per cent. Both the quality and popularity of the service naturally depends on its efficiency, and this unfortunately varies greatly from centre to centre. Shortages of staff, buildings, kitchen and dining-room equipment have severely handicapped many local schemes. These requisites can only be assembled slowly, and meanwhile in many places ideals cannot be reached.

The primary object of the meal is to protect school children from any ill-effect due to defective nutrition, which might follow upon either poverty in the home or inefficiency on the part of the mother. The original aim was to provide a meal yielding about 1000 Cal. and containing a sufficiency of protein, minerals and vitamins, so that even if, at the worst, the child received at home only a poverty diet of bread and jam, no ill-effects attributable to malnutrition would arise. For this purpose a meal consisting of soup, followed by a meat dish with two vegetables and then a pudding is provided.

In April 1957 the standard charge for school dinners was raised to 1s. a day. Provision is made for free dinners in cases of financial hardship ; in 1960 approximately 7 per cent. of the children having school dinners benefit in this way.

In addition to this meal, every child gets one third of a pint (200 ml.) of milk provided free at school. This school milk is available to children at all schools, irrespective of whether they eat their midday meal at school or not. It is usually provided at the mid-morning break, each child having a separate bottle with a straw for drinking.

Experience has shown that only a few of the bigger children eat a 1000 Cal. meal at midday. Detailed surveys of actual consumption of 920 children at three London schools showed average consumption to be 560 Cal. by the infants, 710 Cal. by juniors and 770 Cal. by seniors. In this survey the school meal was estimated to provide 34 per cent. of the calories, 44 per cent. of the protein and 40 per cent. of the calcium needed to supply an adequate diet for the children.

The elaborate school meal service which exists in Great Britain to-day is only possible in a country in which the people are prepared to pay high taxes to provide health services for children. Many countries of the world are not in such a position and school meal services often have to be cut to a much smaller pattern. This problem was discussed by an FAO Committee from the rice-eating countries of Asia, which met in the Philippines (FAO, 1948). The Committee recommended the following type of free meal for school children in the tropics :—

	Oz.	g.
1. Cereals (cereals available, such as lightly milled rice, high extraction wheat, millets or other cereals)	$2\frac{1}{2}$	75
2. A pulse (*e.g.* peas or beans)	$\frac{1}{2}$	15
3. Small fish of which the whole body is eaten (such fish provide calcium)	$\frac{1}{4}$	7
4. Vegetable (green leafy vegetables preferred)	1	30
5. Oil (preferably an oil containing carotene)	$\frac{1}{4}$	7
6. Salt	$\frac{1}{6}$	5

The committee added : " A meal of this kind will provide about 400 Cal. and will contain all the essential nutrients. It should be regarded as illustrating the general pattern of a cheap school meal, and may of course be modified in various ways in accordance with local conditions and the availability of various foods. For example, a greater amount of vegetables might be included, or fruits might be supplied as an alternative to vegetables. Nutrition workers in the different countries can give advice on such questions.

" When facilities are not available for the distribution of full meals, specially prepared buns, cakes, *chapatties* made from flour, food yeast, and other ingredients such as powdered small fish may be found satisfactory. The type of meal which can most suitably be supplied in school feeding programmes will depend on local circumstances."

We can only give a brief outline, such as the above, of the scope of school meals in the tropics. Mention has already been made of the great achievement of UNICEF in providing 4 million school meals daily in Europe, China and other countries. It is the opinion of school medical officers throughout the world that an extension of school meal services is always associated with a rise in the level of child health. School meals are now an integral part of every good public health service. We cannot here discuss the many difficulties in administration ascribable to lack of trained staff, lack of suitable buildings and lack of finance. A full monograph on the subject has been published (FAO, 1953*b*). Doctors, wheresoever they be working, should use their influence to help inaugurate or extend school meal services and smooth out administrative difficulties when necessary. In these ways a positive contribution to child health can be made.

As a postscript, it may be added that school meals can be more than a physiological insurance provided by society against nutritional deficiencies in the home. They provide an excellent opportunity for health education. Pupils, especially the older girls, can learn by taking an active part in the preparation of the meals. A knowledge of food values and cooking methods can be imparted. The meal should also provide an opportunity for instruction in personal hygiene, such as cleanliness of the hands. In all countries there are homes in which food is eaten under dirty and unhygienic conditions. If children feed under good conditions at school, they will expect good conditions at home and some may be able to pass the lessons on to their parents. " It is better to eat nice meals than nasty," writes W. H. Auden. ' Nice meals ' add to the social life. Children can be taught to appreciate them. To do this entails the appointment of qualified and experienced dietitians, skilled cooks and teachers who are able to train scholars to take an active part in—and share the responsibility for—the success of school meals.

Industrial Canteens

Those who perform heavy physical work must of necessity consume large amounts of foods of high energy value. Workers in heavy industry, if a choice is available, often prefer to take a proportion of this extra energy in the form of animal protein, although there is no evidence that this is a physiological necessity. In many industrial firms the managers have for long realised the importance of satisfactory midday meals to the working man's efficiency and have provided canteens and restaurants for their employees. On the outbreak of the Second World War and the introduction of rationing in Great Britain, what had previously been the policy of a few enlightened firms was made compulsory by law. In 1940 the Ministry of Labour passed an order enabling the Minister to enforce the establishment of a canteen at any factory employing more than 250 people on munitions or other work on behalf of the Crown. This was extended in 1943 by the Factories Canteen Order, which abolished the limitation to factories employed on Government work and authorised the provision of canteen facilities for people employed on docks, building sites and collieries. Canteens at collieries became the responsibility of the Ministry of Food.

The number of factory canteens before the war was probably between 1000 and 2000. In May 1945, a survey showed that there were in Great Britain 18,900 industrial canteens of various types and these were serving 8 million meals a day. No information is now available about the number of industrial canteens in the country ; they are certainly numerous and appear to be a permanent feature of British industrial life. Throughout the world, progressive firms are providing canteens for their workers and in a few countries besides Great Britain, governments have at times enforced firms to provide canteens. The more enlightened managements realise the importance of providing their workmen with proper accommodation for meals and rest. In many firms the canteen is a real source of pride and great trouble is taken to make the meals attractive. Managements often subsidise canteens by bearing part of the cost of the catering staff, and the provision and replacement of equipment. In consequence, industrial canteens usually provide meals which are cheaper than those served in commercial restaurants. In some countries the government itself runs popular restaurants, providing nutritious meals for workers at low prices.

Special problems may arise in industry in the feeding of night-shift workers, adolescents and others. Full information is available in a small monograph on industrial nutrition by Pyke (1950).

ENRICHMENT OF FOODS

With the great increase in knowledge of the chemistry of foods it has become possible to increase the nutritive value of certain foods by adding to them quantities of vitamins or minerals or amino acids which are the product of the chemical factory. Such foods are said to be enriched or fortfied. Hitherto bread and vegetable oils have been the foods most frequently fortified. The details have been given and discussed in Chapters 17 and 20. Here only a few generalisations on the possible biological consequences of fortification are given. First, it can be stated that there is no evidence that such artificial fortification does any direct harm. Indeed under certain circumstances, when supplies of a natural food—rich in a particular vitamin or mineral—are limited, then it may greatly improve the nutritive value of a diet if an alternative food, itself of less nutritive value, but appropriately fortified by the chemist's skill, is made available. A possible exception to this generalisation is the addition of vitamin D in excessive amounts to cereal preparations and dried milks for infants. Such additions may be partly responsible for the disease, hypercalcæmia of infants (p. 166).

Secondly, a warning should be given against too wide an application of this principle. So great is the chemical skill of the modern food technologist that it is possible that many artificially prepared foods, enriched so as to appear on analysis to be of as high or even higher nutritive value than natural foods, may be put on the market. Skilful advertising may create a large demand for such foods. The danger of such a procedure lies in our ignorance of suitable methods of assessing the nutritive value of foods. Chemical analyses can only provide information about the known factors. Almost certainly there are important vitamins about which we know nothing. The biological effects of a vitamin, at present unknown, are not likely to become immediately obvious. They may well be concerned either with reproductive efficiency or the retardation of the degenerative processes normal in old age. Biological tests for either of these processes are, of necessity, extraordinarily difficult. Neither chemical nor biological analysis can be sufficiently complete to justify the statement that an artificial food, suitably enriched, is of equal nutritive value to a natural food. For these reasons, there must always be a *caveat* in the recommendation of the use of any enriched food on a large scale.

Thirdly, a policy of enrichment demands a competent chemical industry behind it. In many of the underdeveloped countries of the world, this means dependence on external assistance. It is clearly unwise for any country to embark on a food policy which demands the assistance of a foreign industry except on a temporary basis. Such assistance can readily be cut off either by war or other economic disturbance.

It should be clear that each case of enrichment must be judged on its merits and the ' pros ' and ' cons ' carefully weighed. Because it may be good to enrich vegetable oils with fat-soluble vitamins, it does not necessarily follow that it is good policy to enrich cereal products with the B group of vitamins or with amino acids. What is sound nutrition policy in one country is not necessarily so in another.

EDUCATION

If a family is not taking a satisfactory diet, this must be due either to poverty or ignorance. The importance of the latter is clearly indicated by Cicely Williams (1954*b*) in an excellent article which gives the following examples to show how far negligence and ignorance demand consideration.

> " Even in a country such as England, ignorance and carelessness are still a cause of malnutrition. In a survey of Birmingham school-children in 1938, less than 40 per cent. of the cases of malnutrition were due to economic poverty.
>
> " In the Gold Coast in 1929-35, in areas where kwashiorkor . . . was common, there was almost no poverty. Less than 1 per cent. of the families had so little money that they could not afford to buy tinned milk when advised to do so.
>
> " In East Africa, where kwashiorkor is alarmingly common, there are places where meat and milk are available but the women and children do not get them. The women are told that if they eat eggs they will become sterile, if they eat fowls they will crow, if they eat goat they will grow beards. They may eat only cattle. And often the cattle are kept as tokens of wealth. Though they might improve nutrition they become, as they often do in India, mere parasites on the land.
>
> " India is a more difficult problem. In many communities there is an intense religious objection to taking life. Even an egg is taboo. But there are still many improvements that can be made to a vegetarian or lactovegetarian diet by making more use of green leaves, by preparing flour from mango seeds, and by cooking the wheat or rye flour or pulse as a porridge or *sugi* instead of presenting them to the dyspeptic pot-bellied toddler as tough leather *chapatties*.
>
> " In Ceylon malnutrition usually is due not to the shortage of food but to ignorance of the use of food, particularly ignorance of the needs of the pre-school child (de Silva, 1951).
>
> " Among the Malays, buffalo's milk is often to be had, but it is drunk mostly by the old people and not by the children. Anyhow it is considered inelegant to admit that one is drinking milk from a buffalo and not from a tin.
>
> " Even among the millionaire Chinese and Indians nutritional disasters occur from ignorance of the use of food. Yet many of them are willing and anxious to improve their food habits when knowledge is given to them. So

far, in India and China, the orthodox medical profession has made little effort in nutritional education, while commercial firms and charlatans have done a good deal to exploit both the ignorance and the avidity for information."

Education in nutrition is especially needed in countries where food habits are changing rapidly. In all countries of the world food technology is enlarging the variety of foods available. An increasing proportion of the world's population is moving off the farms and into the towns. Urban diets always and unavoidably differ from rural diets in some respects. The urban housewife, once she is just above the poverty level, has some choice in the food which she provides for her family. To choose wisely she needs some education.

Most primitive people lead lives which are controlled by irrational taboos. Many of these are concerned with food, especially in Africa. Taboos frequently restrict the diet of the pregnant woman and nursing mother, and the adult male gets the best from the family pot. Extensive education programmes are overcoming ignorance in such communities. The importance of understanding people's attitudes to health and disease, food and diet is at last being appreciated. A housewife's attitude, even in the West, may differ very markedly from the concepts acquired by a college-trained doctor or nurse. Dorolle (1953) has done well to insist on the importance of Social Anthropology as a background to medicine. People will only appreciate and trust medical treatment or food which they understand or think that they understand. Good health cannot be thrust upon a community.

Feeding habits are closely associated with emotions, and emotional disturbances can give rise to such obvious nutritional disorders as anorexia nervosa. The fact that our food is strongly linked with our emotions makes all food education a difficult task.

The techniques of food education are many and varied. They have been admirably described and reviewed by Jean Ritchie (1950). Methods must vary widely under different circumstances. Personal instruction in the home or the clinic, discussion group lectures with films or film strips, exhibitions, newspaper articles, radio and television programmes can all contribute.

The following examples of different approaches are taken from Miss Ritchie's monograph. Plates XXIV to XXIX show examples of nutritional education at various levels.

1. The agricultural approach : Iran

Here the Minister of Education of Iran asked for the services of experts to help improve conditions in the rural villages. He was fortunate to get the services of Lyle Hayden, an American agricultural teacher. He settled in Gala—a remote village composed of windowless huts. Flies swarmed on the dung heaps ; it was hot (temperatures up to 43 ° C.) and dusty. There was much sickness. Only two of the inhabitants could read. In this semi-desert, water was the one thing that could arouse the people's imagination. Using his geological knowledge, Hayden was able to find water at 189 feet and set up a new well. Thereafter he became a hero and the peasants listened to him. With the help of the Minister of Education he was able to organise practical instruction in this and nearby villages. Teaching went on in the fields and in the mud huts. Vegetable gardens were cultivated, flocks of chickens were reared, agricultural implements were repaired, children's playgrounds were built. As a result of Hayden's practical agricultural stimulus, knowledge became something to be desired and the health and well-being of the people, especially the children, improved in consequence.

2. The rural school approach : Guatemala

To supplement the strictly academic education in rural schools, the Republic of Guatemala, with the aid of the Inter-American Educational Foundation, set up an organisation for teaching reading, writing and arithmetic in close relationship to problems of health, nutrition, agriculture and home improvement. The first need was to train the teachers. Schoolmasters were given leave of absence from their schools to attend 3-month courses. Longer courses were arranged for specialised teachers. Now there is a well-organised system of instruction in the rural schools whereby children learn things of practical value. The smaller ones may keep chickens or grow flowers and vegetables. They learn to boil drinking water, to clean their teeth and to wear shoes to protect them from hookworm. Older children receive simple instruction in nutrition and have responsibility for school gardens.

3. The approach through literacy campaigns : Nigeria

In 1944 Mr E. R. Chadwick, a district administrative officer, initiated a literacy campaign in the eastern provinces. He persuaded the elders of the villages to take an interest in learning to read. This led to an arousal of curiosity and a desire to learn new things. A reading-room was built and this was followed by a maternity home and dispensary. Model latrines, a small market, chicken houses and an attempt to improve the local breed of fowls came later. Citrus trees were planted in village centres. Women's co-operative societies were formed. Here it was demonstrated that in underdeveloped countries education proceeds best as a whole. Nutritional education is best given as part of a general education.

4. The citizen association—government approach : the Netherlands

In the years 1928-1938 the food situation was adversely affected by economic depression, particularly in rural areas. Two organisations were set up—the Rural Institute for Domestic Information and, in the town, the Commission for Domestic and Family Information. In the country the Institute employs women nutrition teachers. Work is carried out by courses for housewives and house-to-house visits. Courses, which may be given in a house or inn, include some simple nutrition theory, cooking demonstrations, menu-planning with local foods and instruction in the growing of foods and vegetables. A central office supplies films and other teaching aids.

In the towns, local committees control teachers who organise courses, demonstrations and film shows. In the smaller towns the work is done by volunteers. The low-income families are the most difficult to reach. Social workers and district nurses, when they make home visits, encourage families to attend courses and give them advice and literature.

5. The home-economics approach : Puerto Rico

The Home Economics Department of the University stimulated by Lydia Roberts has played a big part in education in Puerto Rico. A nutrition committee with representatives of many government and university agencies was set up. This committee has been active in promoting the use of dried milk, the encouragement of the use of yellow sweet potatoes, various types of green vegetables, ripe papayas and mangoes. Agricultural extension workers are encouraging the production of these foods. Fruit trees are being planted along the roadsides throughout the island. The deficiency of protein is being attacked by a rabbit-breeding project and by education to increase the use of pulses. Nutritional education is being carried out through school lunches.

These are examples of the diversity of ways in which education in nutrition can be brought about. In Great Britain during the Second World War an enormous educational programme was introduced with the object of instructing the public how best to use the limited food which was available. This was for the most part organised by the Ministry of Food; there can be little doubt that it contributed to the general health of the country during and immediately after the war. Many of the posters and advertisements were designed with skill and imagination. Experienced and competent people undertook innumerable lectures and radio talks. The Ministry of Food's handbook *The Manual of Nutrition*, originally written by Dr Magnus Pyke, remains a best-seller. Perhaps the programme was slightly overdone. Certainly a reaction has set in and the general interest in nutrition is now in temporary decline. Those who grew up between 1940 and 1950 may well have thought that they had been more than sufficiently instructed in elementary nutrition. However, a new generation of young people are now becoming parents who were not exposed to this teaching and many of these may well be inadequately informed how to feed and bring up a young family. Initiative now lies with local schools, technological colleges and public health departments, whose duty it is to reawaken an interest in nutrition in Great Britain.

In the U.S.A. nutrition education is widespread. The very large proportion of girls who receive a college education contributes to this. In most girls' colleges some form of biology and health education is given, and American women, as a result, have a good general knowledge of the relative values of foods. In the U.S.A. the enormous advertising programmes of the big firms in the food industry have an important educational role. For the most part this is beneficial, but there are on occasions highly misleading advertisements. The women's journals usually carry good articles on health, the care of children and nutrition in general; the information given is usually accurate and these articles no doubt are a potent educational force.

Health education helps to assure that the best use is made of available food supplies. The better educated the women of a country, the better will be the health of all sections of the population. The responsibility for this education rests in part with Educational Authorities and in part with Medical Authorities. In a well-developed country the former should be responsible for most of the formal instruction. In girls' schools and colleges the elementary principles of dietetics and good housekeeping must be explained to every future mother and housewife.

In underdeveloped countries a great responsibility rests on the Maternity and Child Health Services. Doctors and nurses, especially those well trained in pædiatrics, can gain the confidence of the people. The role of the hospital is most important, as Dr Cicely Williams stresses. She writes (1962): ‘ Some of the most valuable work on nutrition has come from hospitals in East and West and South Africa, Guatemala, India, Malaya and Jamaica. Disease can be prevented and the people educated in prevention when cases can be studied, diagnosed, treated and then followed up efficiently. These hospitals are few and far between; but it is in and from them—and nowhere else—that the problems can be most readily appreciated. It is through good treatment and follow-up that health education in nutrition is best given.’ Curative medicine can open the door for preventive medicine. In underdeveloped countries there should be no divorce between these two medical services. In particular obstetrics and pædiatrics provide a fine opportunity for the practice of both branches of medicine. Maternity and Child Health Clinics should be centres both for healing and education.

Training of dietitians and nutritionists

Finally, a word must be said about the training of specialists in dietetics and nutrition. The profession of dietitian is steadily gaining recognition. In several countries professional associations are engaged in the twofold task of raising standards and status. In the U.S.A. and in Canada all dietitians must have a Bachelor's degree from an accredited college. Courses for such degrees are based on a syllabus which divides the period of study between fundamental sciences such as chemistry, biochemistry and physiology, and the practical work of hospital and public health dietetic departments. In Great Britain dietitians at present must train for 1 to 1½ years in a dietetic department of a large hospital. A prerequisite for acceptance for training is either a B.Sc. degree, a diploma in domestic science or a state registration as a nurse. The British Dietetic Association is actively concerned with educational policy and the provision of adequate facilities for study. London University has established a B.Sc. degree in nutrition, for which instruction is given in Queen Elizabeth College. Starting in 1962 London University will hold a one-year course for a postgraduate diploma in nutrition. This course will be open to graduates of universities and colleges from the United Kingdom and overseas. It will cater for students with varied educational backgrounds, including agriculture, food technology, the social sciences and medicine.

Although in most countries the doctor is widely accredited as an expert in nutrition, in fact, nutrition is given only a very small place in the curriculum of most medical schools. It is uneasily divided between departments of biochemistry, physiology, clinical medicine and public health. Standard textbooks on these subjects for the most part deal with nutrition inadequately, presumably under the impression that it is covered elsewhere. Postgraduate instruction in nutrition is limited and often confined to courses for the Public Health Diplomas. In many of these courses the time allotted to nutrition is only a few hours and the presentation little more than a recapitulation of undergraduate teaching in physiology. In some schools, however, excellent courses are given. In particular, the Harvard School of Public Health, with a distinguished staff of nutritionists under Dr F. J. Stare, has for several years given first-class postgraduate instruction.

The Nutrition Research Laboratories in Coonoor in South India began in 1935 under Dr W. R. Aykroyd to give informal courses in nutrition lasting for 2 to 3 months. The course was originally intended primarily for doctors ; but chemists, agriculturists, educationists and others attended. Recently these laboratories have been moved to Hyderabad where the courses have been continued first by Dr Patwardhan, at present responsible for the nutrition research programme of WHO, and now by Dr C. Gopalan.

FAO and WHO, sometimes with the co-operation of UNICEF, CCTA (Commission for Technical Co-operation in Africa south of the Sahara) or the ICC (International Children's Centre, Paris) organise training courses and seminars on an international basis in the different regions of the world. Several of these have been for French-speaking people working in Africa and the Middle East. A feature of these courses has been the emphasis on field work. They are a means of training numbers of people in the practical approach to nutritional problems. Students come with widely different backgrounds of training. The presence of doctors, agriculturists, chemists, educationists, social workers and others in a common class, each approaching the problems from a different angle, is itself of great educational value. This has been demonstrated at international seminars on education in Health and Nutrition held in the Philippines in 1955 and in Germany in 1959. The reports of these conferences (FAO, 1956 ; FAO, 1960) should be read by all interested in teaching nutrition.

CHAPTER 52

THE POPULATION PROBLEM

MALTHUS

IN 1798 Malthus published his famous *Essay on the Principles of Population as it affects the Future Improvements of Society with Remarks on the Speculation of Mr Godwin, Mr Condorcet and other Writers.* Mr Godwin achieved some fame as the father-in-law of the poet Shelley, over whom he had considerable influence. At the end of the eighteenth century Godwin had seen the results of the great improvements that had recently taken place in British agriculture and had a prophetic glimpse of the possibilities for wealth that the Industrial Revolution was to bring forth. He considered that with these material aids the perfecting of human society was a practical proposition. Malthus' father, a Surrey squire, was a disciple of Godwin and the essay on the principles of population is perhaps a reaction against excessive paternal optimism. The main argument is that any temporary or local improvement in human living conditions will increase a population faster than corresponding agricultural developments can increase the food supply. Hunger and starvation with their associated war and pestilence will then automatically set back the advance and check the population growth : these disasters are inescapable features of human society, which by its very nature can never be stable. Such, in brief, is the Malthusian dilemma.

DEATHS, BIRTHS AND POPULATION GROWTH

Table 52, 1, prepared by Benjamin (1962) from United Nations data, shows how the population is growing in all regions of the world. It will be seen that in some regions birth-rates lie between 40 and 50 per 1000. Death-rates vary widely, but in many relatively healthy countries have fallen to 10 per 1000 or less.

Table 52, 2 is an estimate of the expected growth of population by 1975 and 2000. It is also prepared by Benjamin and is ' based on medium assumptions.' There is little reason to doubt that, in the absence of major catastrophes, by the year 2000, less than 40 years ahead, there will be twice as many inhabitants of the world as there are to-day. This means that there will be about 3000 million extra to feed.

It has been pointed out in Chapter 49 that agricultural expansion in many countries is barely keeping pace with the present growth of population. If Benjamin's forecast as quoted above is accepted, the agricultural problem becomes even more serious. To what extent is it possible to control the numbers of the world population by active social

TABLE 52, 1. *Population,* 1959 *and annual average birth, death and population growth rates, by regions,* 1950-59

	Population mid-year 1959 (millions)	Birth-rates*	Death-rates*	Population growth-rates (per cent.)
WORLD	2907	36	19	1·7
AFRICA :				
Northern Africa . .	78	45	26	1·9
Tropical and Southern Africa . . .	159	47	28	1·9
	237	46	27	1·9
AMERICA :				
Northern America . .	196	†25	†9	‡1·8
Middle America . .	65	†45	18	2·7
South America . .	137	42	19	2·3
	398	34	14	‡2·1
ASIA :				
South West Asia . .	74	46	21	‡2·5
South Central Asia . .	546	44	26	1·8
South East Asia . .	208	44	23	2·1
East Asia . . .	794	†39	†21	1·8
	1622	42	23	‡1·8
EUROPE :				
Northern and Western Europe . . .	141	†18	†11	‡0·7
Central Europe . .	137	†19	†10	‡0·8
Southern Europe . .	145	†21	†10	‡0·9
	423	19	10	0·8
OCEANIA	16	†25	†9	‡2·4
U.S.S.R.	211	†25	†8	1·7

* Birth-rates and death-rates are per 1000 population and are annual averages for 1955–59.

† Weighted average of recorded rates.

‡ This rate reflects the combined effect of natural increase and migration.

and health policies ? To what limits can agricultural production be increased ? Before attempting to answer these very important questions, it is necessary to consider briefly some of the factors affecting death-rates and birth-rates.

POPULATIONS WITH HIGH DEATH-RATES AND HIGH BIRTH-RATES

For about a thousand years—from the beginning of the Middle Ages to the middle of the eighteenth century—the population of Europe

TABLE 52, 2. *The expected growth of population to 1975 and to 2000 in different regions*

Continent	Population (millions)		
	1959	1975	2000
World . . .	2907	3828	6267
Africa . . .	237	303	517
N. America . .	196	240	312
Latin America .	202	303	592
Asia . . .	1622	2210	3870
Europe . . .	423	476	568
Oceania . .	16	21	29
U.S.S.R. . .	211	275	379

probably remained more or less constant. There is also no evidence of any important permanent changes in the number of inhabitants of Asia during this period. This stability existed because birth-rates in all countries were probably over 40 per 1000 of the population yearly. This rate of reproduction probably represents the maximum of which the human species is capable. Yet it was only just sufficient to make up the losses due to war, famine and disease. For the biological survival of man, it was necessary that every adult woman should be as fertile as possible. The organisation of society in all countries, both in the East and in the West, was such as to encourage fertility. In this, all the great religions of the world, Confucianism, Hinduism, Judaism, Christianity and Mohammedanism, have co-operated. An early marriage and a large family was the avowed aim for every girl. Those who achieved this aim received both social and religious approval. The sterile woman was an object of scorn and derision. This attitude to women was all but universal until 200 years ago. Under the circumstances it was sensible—indeed essential—if mankind was to survive. However, now under very different circumstances, it still persists to some extent in all countries and in many it remains the dominant concept of woman's role in society.

THE FALL OF DEATH-RATES IN EUROPE IN THE EIGHTEENTH CENTURY

In the middle of the eighteenth century the death-rate in most European countries began to fall and has for the most part fallen steadily ever since. The reasons for the start of this fall are uncertain. Popular opinion, and even eminent historians such as Trevelyan (1942), often ascribe it to the benefits of the new medical science. In fact therapeutics has only advanced sufficiently to have a significant effect on death-rates within the last 50 years. Indeed it is only in the last two decades, with the widespread use of antibiotics and insecticides, that medical science has seriously affected demographic processes and so caused renewed interest in the Malthusian dilemma. The fall in death-rates in Europe in the eighteenth century can be attributed in part to the spread of religious toleration. Toleration put an end to the lethal civil wars of religions in the previous centuries. Then law and order could be more easily maintained and so roads and communications opened up. In addition, new improved agricultural methods and the introduction of the potato from America markedly reduced the effects of bad agricultural seasons and virtually abolished European famines which had hitherto caused heavy losses of life in most countries (Salaman, 1948). Further, both bubonic plague and smallpox, which caused so many deaths in the sixteenth and seventeenth centuries, declined in Europe and were no longer such important factors in the population equilibrium. The effect of a natural decline in the virulence of smallpox was increased by the discovery of vaccination by Jenner.

The Fall of Death-rates in Asia and Africa

In Asia a similar fall began in the middle of the nineteenth century, often following upon a period of colonial rule. Law and order gradually replaced civil war ; there were enormous increases in transport facilities and by the end of the nineteenth century famine, plague, smallpox and cholera were in large measure controlled. These factors all operated most markedly in the countries which became subjugated to European or Japanese metropolitan powers. Whatever the demerits of colonialism, it has always been associated with a fall in the death-rate and a rise in the numbers of the colonial peoples.

In most underdeveloped countries, including Africa, death-rates only began to fall after 1925. In many countries a dramatic fall first occurred after the Second World War (United Nations, 1954) and was brought about by the increased economic prosperity, the widespread use of insecticides and also by antibiotics.

The Problem in the Twentieth Century

In several countries of the world, death-rates are now just below 10 per 1000 of the population yearly. It would seem unlikely that advances in medical science, even if fully applied, can lower the death-rate in any country substantially below this figure. However, there is no reason why death-rates in all countries should not fall to this level, provided the people obtain a sufficiency of food and acquire good medical services. Indeed a death-rate of 10 per 1000 is a legitimate aim for all responsible governments. It represents a target which satisfies the natural desire to preserve life and it has been demonstrated to be practically possible.

It is, however, quite incompatible with birth-rates over 40 per 1000 and unfortunately many countries still have social organisations and religious customs which operate powerfully and are geared to these high birth-rates. The gears are not however inevitably fixed. Indeed, whenever there has been a fall in the death-rate, this has been succeeded after an interval by some fall in the birth-rate. The latter, however, always lags behind the former. In the interval the population inevitably increases. Can this lag be reduced and the fall in birth-rates accelerated ? If so, can the increase in population be kept within the measure of the increase in agricultural production ? Only in this way can there be an escape from the dilemma of Malthus. Agricultural science must keep up with medical science. If in any country the tempo of the introduction of new medical and civil engineering techniques greatly exceeds the tempo of corresponding agricultural improvements, only disaster can follow.

Population Control

Ever since ancient times there have been individual men and women who have deliberately limited the size of their families. Birth control is not new, but until the twentieth century it was limited to a small minority of parents, usually belonging to intelligent families. A most important factor, which restricts the birth-rate, is the delay in the age of marriage. A girl who is married at 13 or 14 is likely to have more children than one whose marriage is delayed until after she is 20 years of age. The extension of higher education to women has already had an important effect on birth-rates in many countries and this influence is spreading fast.

Techniques for enabling sexual intercourse to take place without ensuing pregnancy, based on either mechanical or chemical means, have been developed slowly over the last 50 years. They are still far from satisfactory though there are indications that important developments are taking place (see p. 755). An important section of the human community, the Roman Catholic Church, however, objects to the use of all such methods, which it considers to be morally wrong. This view is not held now by the Protestant churches. However, there are many countries in which the Roman Catholic Church has a dominant influence in the Government. In these countries research and teaching in contraceptive methods is forbidden and in some the sale of contraceptives is illegal. On the other hand, there are many who consider that the widespread distribution of modern contraceptive knowledge is an urgent necessity and that this presents a major Public Health problem. When, however, the matter was discussed at the Fifth World Health Assembly in Geneva in 1953, there were extreme divergences of opinion amongst the delegates and the Assembly had to agree that this was a subject upon which no action could be taken. The many delegates from Roman Catholic countries were unable to accept the view that birth control was a proper subject for study by an international health organisation.

India is a secular state in which the Government is attempting to deal with agricultural and industrial development in a series of Five Year Plans. In a preamble to the Second Five Year Plan it is stated :—

> "The recent increase in the population of India and the pressure exercised on the limited resources of the country have brought to the forefront the urgency of family planning and population control. The application of medical knowledge and social care has lowered the death-rate while the birth-rate remains fairly constant. . . . Population control can be achieved only by the reduction of the birth-rate to the extent necessary to stabilise the population at a level consistent with the requirements of national economy. . . . A reduction in the rate of growth of the population must be regarded as a desideratum. . . . Family planning or spacing of children is necessary and desirable in order to secure better health for the mothers and better care and upbringing for the children."

This clear statement of the problem in a Government report is unusual. In India 802 family planning clinics were opened in the first three years of the Second Five Year Plan, and 281 were added in 1959-60. It is too early yet to assess the effects of this programme, but it has been well received by the bulk of the population. Additional people are being trained to disseminate knowledge of the need for, and methods whereby, the size of the family can be regulated. The Second Five Year Plan included the provision of Rs. 54·7 million (about £4,000,000) for these objectives. This is more than a modest approach to the problem, and we must applaud the sincerity and judgment with which the Indians are attempting to find possible solutions.

Japan, like India, has an important population problem of which the Government is fully aware. After the defeat of the Empire in 1945 birth-rates were far higher than death-rates. In addition, about 5 million Japanese subjects were compulsorily repatriated to the homeland from former colonial territories. Faced with increases in the population far greater than any possible increases in agricultural production, the Government introduced the legalisation of abortion in 1948. In 1954 over 1 million abortions were induced. In this they were following the example of Soviet Russia 25 years previously. In Russia this experiment was not successful and the legislative sanction of abortion was soon removed. The Japanese have also found legalised abortion both damaging to the physical and psychological health of women, and also relatively ineffective in reducing the increase in population. The Japanese Government has encouraged studies of the attitude of the people to family limitation and the possibilities of education. Successful family planning programmes have been organised and implemented. Japan now appears to be approaching population stability at two and a half to three times its level of a century ago. Industrialisation, urbanisation, rising standards of living and of education, and the Government's population policies have fostered the conception of family planning.

In *Africa south of the Sahara* a rapid fall in the death-rate has only recently occurred. Unlike the situation in the Far East, the population density is still low. Education and technical knowledge is spreading rapidly. The economic potential of the continent is great. It is to be hoped that the governments of the many new African countries will profit from the experience of others and institute family planning as an integral part of their development programmes.

The Public Health Approach

Population control can probably best be approached indirectly. Exhortation to uneducated women to limit their families is unlikely to be effective. Particularly in areas where the infant mortality rates are high, it is quite useless to preach birth control. It is natural for men and women to desire healthy children to take their place in life and to provide for their parents in old age. In societies where the women are ignorant of the elementary laws of hygiene and do not know either how to raise their children properly or to protect them against the common infectious diseases associated with dirt and squalor, a woman must produce many children if she is to expect to rear even two or three up to adult life. It would appear, however, that the parental instincts—a very real biological factor—are usually satisfied by two, three or four *healthy* children. In most countries, both in the East and in the West, it is probable that most women who have successfully produced a few healthy children seek ways and means to prevent the arrival of more. Poverty and ignorance are associated with high birth-rates and knowledge and a desire for social security with low birth-rates. If women can be shown how to raise a small healthy family, then most of them will actively seek advice as to how to prevent more arrivals. It is easy to teach people who desire knowledge.

If this reasoning is accepted, it follows that the first step in an attack on the birth-rates must be through the Maternity and Child Health Centres. In these Centres women can be taught mothercraft ; nutritional education is, of course, a most important part of such teaching. When the Public Health Nurses have successfully educated the majority of the women in a community how to rear healthy children, then the demand for advice on contraception will inevitably and automatically follow. As in the case of so many other aspects of preventive medicine, the Maternity and Child Health Departments can provide centres from which new ideas must spread out amongst a people. It is impossible to underestimate the importance of this aspect of medicine to-day. This is a lesson that has to be impressed on politicians and others who control and distribute funds for health projects in all countries, but particularly in backward and illiterate communities. In an earlier chapter we pointed out the importance of the water engineer in determining the world's future. Water engineers and Public Health Nurses may well have as important a role in the future well-being of mankind as have atomic scientists.

ORAL CONTRACEPTIVES

There have been a great many folk methods of contraception employed since time immemorial, such as the rhythm method and coitus interruptus. Unfortunately all such apparently simple methods have so far proved either unsatisfactory or ineffective. Until recently all effective modern methods involve the placing of some kind of barrier, either mechanical or chemical, between the sperm and the ovum. The use of these methods necessitates a certain modicum of intelligence and some knowledge. In their present forms they are not suitable on a large scale for people who are both poor and ignorant.

Recent research has led to the development of contraceptives which can be taken by mouth and render a man or woman temporarily sterile. The most important of these are substances that inhibit ovulation. There are many steroids that will do this, but most have undesirable side-effects. Over 200 new steroids have been tested on laboratory animals ; one, norethynodrel, if combined with a small dose of a synthetic œstrogen, has been shown to be effective and safe as a contraceptive in trials on married women.

Pincus and his colleagues (1959), working in Puerto Rica and Haiti, have been pioneers in this field. Trials have also been conducted in the U.S.A. and in England. The latter first started in Birmingham in 1960 under the auspices of the Family Planning Association. Mears (1961) provides a useful summary of this and other more recent British trials. There is little doubt that 2·5 to 5 mg. of norethynodrel, combined with a suitable dose of œstrogen, such as 0·1 mg. ethinylœstradiol, if taken daily for 20 days beginning at the fifth day after the start of menstruation, will render the great majority of women sterile for that menstrual period. Adverse side-effects such as intermenstrual bleeding or amenorrhœa, are usually absent or can be easily controlled. On stopping the drugs fertility promptly returns. The present cost of the pills in Great Britain is twelve shillings per month. If the cost of oral contraceptives can be lowered and the method becomes practical for, and acceptable to, women of the poorer classes in countries where the population is increasing rapidly, it may have a profound effect on the future of mankind.

There are also indications that it may be possible to render men sterile temporarily. Thus phosphorylated hesperidin apparently inhibits the enzyme hyaluronidase, which assists the sperm to liquefy the gel surrounding the ovum, so enabling it to enter and fertilise the ovum. This substance is apparently innocuous when taken by mouth and preliminary trials have indicated that it may prove a practical oral contraceptive. A documented review of this subject has appeared in the *Lancet* (1956). Only within recent years has research on contraception become 'respectable.' Money and talent are now becoming available in many countries and, as indicated above, important new developments have arisen. In our opinion the need for further experimental work both in laboratories and clinics is great.

THE AGRICULTURAL OUTLOOK

In the immediate future a satisfactory food supply for each individual in the world is more likely to be achieved by an increase in agricultural production than by a decline in the numbers to be fed. To what extent can the agricultural resources of the underdeveloped countries in the world be improved ? According to FAO the yield of food from the present cultivated part of the world's land surface could be increased between 50 to 100 per cent. by the use of better methods of agriculture, the application of suitable fertilisers, the control of pests and the improvement of storage conditions. The present arable area of the earth's land surface could be increased by about 100 per cent. The catches of fish from the oceans, lakes, rivers and ponds could be increased many times. To quote Brock (1961) " The potentialities for the future in improved food supply are difficult to estimate, but anyone who says that anything is impossible is likely to find himself embarrassed within a decade."

Numerous books have been written on this subject. The most optimistic of these has been written by a Brazilian doctor (de Castro, 1952), who sees almost unlimited possibilities for developing the uncultivated regions of the world. It is true that of Brazil's 2000 million acres, only 2½ per cent. are as yet cultivated. Canada is a little larger in area than Brazil and only 8 per cent. of the land is cultivated. Yet the technical difficulties of developing the jungle land in the Amazon basin, or the potential agricultural resources in the sub-Arctic, are immense.

Ritchie Calder (1952) is another optimist, who has described brilliantly the start made to reclaim the deserts of North Africa and the Middle East for agriculture. French and Israeli scientists, water engineers and farmers have already achieved much in these areas. If only they could enlist the co-operation of the indigenous people of the deserts—instead of provoking their hostility—a vast increase in food production would appear to be possible.

Other writers are pessimistic. In Great Britain Sir Charles Darwin in many lectures and articles stated that agriculture will not be able to supply sufficient food for the peoples of the world for much longer, unless something can be done to limit the continual increase in the numbers to be fed. Perhaps the most balanced account of this problem is given by Sir John Russell (1954) in a fully documented monograph. More recently Russell (1960) has restated his views in a popular science journal. He confesses to ' tempered optimism ' and concludes that in the absence of major wars and with the continued investment of capital and brains in agriculture, it is not unreasonable to hope that food production will increase for many years at least as rapidly as in the last decade—and so keep up with the growth of population. However there must be a limit to the capacity of world agriculture and so the dilemma set out by Malthus will always remain real.

CHAPTER 53

FAMINE

AS far back as history records, mankind has suffered at irregular intervals from great famines. In many the disaster has been so great that a million or more people have perished. The enormous advances of science in this century have made the prevention and relief of famine technically very much easier. There is now the hope that mankind has suffered the last great famine. Yet it would be wrong to be too optimistic. As recently as 1943 at least a million people died of famine in Bengal. Subsequently in many parts of the world famine conditions have arisen, but fortunately on a smaller scale.

The worst disasters have occurred when the famine has not been foreseen and the Government has lacked the administrative experience to organise relief. On the other hand there are many examples of foresight which has enabled relief measures to be planned ahead. A well-planned and organised relief service can help a people to survive a period of famine, not without hardship and suffering but at least with no great increase in the number of deaths. A false sense of security has led to too little study of the problems presented by famine. We know of no recent monograph devoted to the general problems of the subject, although there are many books giving excellent historical accounts of particular famines. In this chapter an attempt is made to set out a few general principles.

CAUSES OF FAMINE

These can usually be ascribed to one of four heads.

Widespread failure of crops due to lack of water

In tropical and subtropical countries large numbers of people have lived and continued to live under the yearly threat of drought. A failure of the rains, often in successive seasons, has been a frequent cause of famine. The importance of the science of irrigation in the husbanding and control of natural water has been discussed in Chapter 49. In Asia and in Africa irrigation schemes, often on a vast scale, have made large areas of land practically independent of yearly variations in rainfall. Yet much remains to be done and in many districts throughout the tropics and subtropics bad rains can bring the people to the verge of disaster.

Destruction of crops by diseases and pests

The great Irish famines of the nineteenth century were caused by the destruction of the potato crops by a fungus, which produces a disease known as ‘ the blight.’ Whenever people are largely dependent on a single crop for their main source of food, there is always the risk that the crop may be destroyed by disease, and famine conditions follow. Plagues of locusts can cause great destruction of all crops and, in some parts of the world, these greedy insects are a potential cause of famine (Plate XXI).

Wars and civil disturbances

Wars and especially civil wars have been directly responsible for many famines throughout history. It was mentioned in Chapter 49 that food shortages are an inevitable result of all wars and these can readily lead to famine conditions. Nuclear warfare on a large scale in an industrial country might quickly lead to famine amongst the survivors, through destruction of transport, docks and warehouses.

Great natural disturbances

Floods and earthquakes are a constant natural threat to man in many parts of the world. They can destroy crops, food stores and communications and so cause famine.

Each of these four primary causes is still operative. It is reasonable to suppose that on occasions—and probably unexpectedly—each may again give rise to famine.

EFFECTS OF FAMINE

Literature contains many moving accounts of human suffering during famines. Two of these are given below. The first is a letter from Ireland addressed to the Duke of Wellington on 17th December 1846 (Edwards & Williams, 1956).

“ Having for many years been intimately connected with the western portion of the county of Cork, and possessing some small property there, I thought it right, personally, to investigate the truth of the several lamentable accounts which had reached me of the appalling state of misery to which that part of the country was reduced. . . . Being aware that I should have to witness scenes of frightful hunger, I provided myself with as much bread as five men could carry, and on reaching the spot I was surprised to find the wretched hamlet deserted. I entered some of the hovels to ascertain the cause, and the scenes that presented themselves were such as no tongue or pen can convey the slightest idea of. In the first, six famished and ghastly skeletons, to all appearance dead, were huddled in a corner on some filthy straw, their sole covering what seemed a ragged horse-cloth and their wretched legs hanging about, naked above the knees. I approached in horror, and found by a low moaning they were alive, they were in fever—four children, a woman, and what once had been a man. It is impossible to go through the details, suffice to say, that in a few minutes I was surrounded by at least 200 of such phantoms, such frightful spectres as no words can describe. By far the greater number were delirious either from famine or from fever. Their demoniac yells are still ringing in my ears, and their horrible images are fixed upon my brain . . . the same morning the police opened a house on the adjoining lands, which was observed shut for many days, and two frozen corpses were found lying upon the mud floor *half devoured by the*

> *rats.* A mother, herself in fever, was seen the same day to drag out the corpse of her child, a girl about 12, perfectly naked; and leave it half covered with stones. In another house . . . the dispensary doctor found seven wretches lying, unable to move, under the same cloak—one had been dead for many hours but the others were unable to move either themselves or the corpse. To what purpose should I multiply such cases? If these be not sufficient, neither would they hear who have the power to send relief and do not, even though 'one came from the dead.'"

The second (Hunter, 1868) describes from contemporary letters the scene in Western Bengal in 1770, when it is estimated that 10 million people—or a third of the population—died.

> "All through the stifling summer the people went on dying. The husbandmen sold their cattle; they sold their implements of agriculture; they devoured their seed grain; they sold their sons and daughters, till at length no buyer of children could be found; they ate the leaves of trees and the grass of the field; and in June 1770, the Resident at the Durbar affirmed that the living were feeding on the dead. Day and night a torrent of famished and disease-stricken wretches poured into the great cities. At an early period of the year pestilence had broken out. In March we find smallpox at Moosshedabad, where it glided through the vice-regal mutes, and cut off the Prince Syfut in his palace. The streets were blocked with promiscuous heaps of the dying and the dead. Interment could not do its work quick enough; even the dogs and jackals, the public scavengers of the East, became unable to accomplish their revolting work, and the multitude of mangled and festering corpses at length threatened the existence of the citizens."

Of the many effects of famine, it is practical for purposes of administrating relief to keep three constantly in mind.

Deaths from starvation

It is of prime importance to procure and distribute sufficient food to prevent such deaths. Their number is the one measure of the severity of the famine and the effectiveness of the relief organisation. Old people and young children are particularly liable to die of starvation. Adolescents often manage to survive. Women usually survive better than men.

Panic and social disruption

It is natural for starving people, if there is no food in their immediate neighbourhood, to leave home and go in search of something to eat. If such wandering takes place on a large scale, social chaos is inevitable and all relief work becomes many times more difficult. Families are easily disrupted and only with great difficulty later reunited. If parents die, infants and young children may be found helpless with no knowledge of their family name or the whereabouts of their home or of other relations. Adolescents, if separated from their families, readily form gangs, which are actively opposed to all forces of law and order. Such gangs may be a source of much mischief and the subsequent rehabilitation of the members a very difficult social problem.

The spread of epidemics

Louse-borne typhus has been the great famine disease in Europe, and cholera and smallpox in Asia. But large epidemics of relapsing fever, influenza, tuberculosis, enteric fever—or indeed of any infectious disease—may be associated with famine. In malarious countries famine usually occurs in times of drought and so conditions are unsuitable for the mosquitoes which transmit the disease. When the rains do come, often in excessive amounts, malaria may spread rapidly among the enfeebled survivors of the famine. On some occasions there have been more deaths in the malaria epidemic subsequent to a famine than in the famine itself.

It is unusual to find epidemics of any of the diseases attributable to vitamin deficiencies in a famine, though scurvy may afflict the inhabitants of a besieged city or a desert people.

The rapid spread of infectious diseases among a starving people is attributable to the ease with which the infecting organisms can pass from person to person as a result of overcrowding and the breakdown of normal sanitary arrangements. It is the absence of all hygienic precautions that is responsible for epidemics rather than an increased susceptibility of the starving body to infective micro-organisms (Chapter 56). In many famines far more people have died of infectious diseases than of starvation.

These three effects of famine, deaths from starvation, social disruption and the spread of epidemics, should be constantly in the mind of relief workers. It is important to repeat and emphasise this ; for in a famine there is always more to do than can be done. The time and energy of the workers must be disciplined, for it is easy to be distracted by a charitable heart to a task which may be very worthy yet of secondary importance.

FAMINE RELIEF

Procurement and Distribution of Food

Transport problems

Fortunately for mankind the causes of famine are local. A district, a province or even occasionally a whole country may be involved, but never a whole continent. Stores of surplus food have always been available—somewhere. How to get the food to the right place fast enough is always the fundamental problem. Modern methods of transport have greatly mitigated the effects of famine. The rapid development of railways throughout India in the middle of the nineteenth century facilitated the organisation of relief and was the means of saving many lives.

Ships, trains, aeroplanes, lorries and sometimes bullock carts, camels and other pack animals may be needed. The procurement and organisation of these is the first and most important problem of a relief organisation.

Quantities of food required

The minimum amount of food necessary to preserve human life has been much debated in the past. FAO in 1946 set out recommendations for subsistence and maintenance levels of caloric intake, which are given in Table 53, 1. These figures represent a compromise between physiological needs and practical difficulties. Nutritionists must warn governments that unless food is available at this emergency subsistence level, deaths from starvation and civil unrest are likely. The figures in Table 53, 1 have to be converted into tons of cereal grain. One ton of cereals provides about 3·5 million Cal. This will suffice for about 1850 sedentary males for a day at the emergency subsistence level. To calculate the total food that must be imported into a famine area, it is also necessary to know or estimate (1) the number of people in the area, (2) the amount of physical labour that is required of them, (3) the proportions of women and children, (4) the stores of food already in the area and (5) the probable duration of the emergency. With these data, tables of physiological needs can be converted into statements of cargo space required.

TABLE 53, 1. *Scales of caloric allowances suitable for use in time of famine*

Category	Emergency subsistence level*	Temporary maintenance level†
0–2 years	1000	1000
3–5 years	1250	1500
6–9 years	1500	1750
10–17 years	2000	2500
Pregnant and nursing women	2000	2500
Normal consumers (sedentary)		
Male	1900	2200
Female	1600	1800
Moderate workers	2000	2500
Heavy workers	2500	3000
Very heavy workers	3000	3500

* *Emergency subsistence level* needed to prevent the most serious undernutrition leading to disease and the danger of civil unrest.

† *Temporary maintenance level* sufficiently high to maintain populations in fairly good health but not sufficient for rapid and complete recovery.

Such estimates can be nothing more than guesses unless a recent and reliable census is available. The importance of a census can never be overestimated.

Public works

The growth of the British Empire throughout the eighteenth century compelled civil servants to consider ways and means of distributing food to famine victims. They were greatly influenced by two principles.

The first was that trade was the natural and proper means for the distribution of all goods, including food, and that governments should interfere with trading operations as little as possible. The second was that charity ultimately degrades the recipient, who should if possible pay for the relief which he receives. In the formulation of these principles the influence of Adam Smith was great. His book *The Wealth of Nations* was published in 1776 and his *laissez-faire* economic doctrines were widely accepted at the beginning of the nineteenth century. They greatly affected the organisation of famine relief. It was concluded that the real need of the famine victim was for money. If he was provided with money, food would become available through the channels of normal trade, which would be developed to meet his needs. He could get money if he had the opportunity to work. The solution to the problem was thus the setting up of public works. There has been much experience of the public works system of relief, but it is difficult either to condemn or approve the system whole-heartedly.

In Ireland in 1846-47 and in Bengal in 1943, the system failed to prevent the deaths of hundreds of thousands. It must be added that in both these countries it was administered by local civil servants who were without experience of famine and who were not adequately forewarned. Time and experience are needed to plan and organise public works.

On the other hand, in several parts of India where famine conditions arise owing to failure of the rains, relief works have frequently been the means of helping people through an emergency period without loss of life, but not without hardship and suffering. Here there has been the advantage that the probability of famine was usually foreseen, and experienced local staff was available to plan ahead and administer relief work.

Even under the best conditions, the system has its disadvantages. The food requirements of the people are increased by the physical work involved and also by the walk from their homes to the work sites. Even with the best planning, it is impossible to organise work for all in the immediate neighbourhood. Furthermore, the old and those physically handicapped may be unable to work and so get no relief. Pride may prevent members of the middle classes from undertaking manual labour. Often the work itself is of little value. Road-making has been commonly undertaken and many of the roads have led from ' nowhere in particular to nowhere at all,' in the words of Salaman (1948), an historian of the Irish famine. Useless physical work may be demoralising. Well-planned public works have their place in famine relief under many circumstances, but it is unwise to rely too heavily on them, especially if an experienced supervisory staff is not available.

Public kitchens

Cooked food may be distributed from public kitchens. This is usually essential in a severe famine. Only in this way is it possible to ensure that food reaches those too old, too young or so severely handicapped that they cannot work. Further, it is often impossible to bring into a famine area the foods to which the people are accustomed. The introduction of strange foods, which the people may not know how to cook or prepare, has presented great difficulties in the past. This can be overcome in part by the distribution of meals at special centres.

Price control

It is essential that the prices of such foods as are available be kept within the means of the famine victims. There are always some merchants who are willing to exploit the sufferings of others to their own financial gain. Legislation to prevent any excessive rise in prices is most essential, and direct subsidies on cereal grains and other foods may be desirable. The extent to which prices are kept down is a measure of the efficiency of the government.

MEDICINE IN A FAMINE

The problem before every member of the medical services engaged in famine relief is not ‘ What is there for me to do ? ’ but rather ‘ Of the many jobs to be done, which will save most lives ? ’ In a famine there are never enough doctors or nurses ; hospital beds and equipment are insufficient ; drugs and vaccines are scarce.

Assessment of the state of the famine

The efficient organisation of relief depends upon accurate assessments of the course of the famine. The number of people likely to be in need of relief in the near future must be forecast. This is never an easy matter and there are always those who, for political reasons, seek either to minimise or exaggerate the extent of the distress. Great disasters seldom arise suddenly and without warning. A Public Health Service that can give week-by-week reports on the numbers of deaths and the numbers seeking admission to hospital is invaluable. If possible, the causes of death and the nature of the diseases requiring hospital treatment should be stated ; even if the diagnosis cannot always be precise and accurate, the information is still useful, especially as an indication of the appearance of a new infectious disease. The organisation of accurate medical statistics is thus of first importance.

Observation of the state of nutrition of the people is also valuable. As discussed in Chapter 50, there is no single simple method of assessing nutritional status. Nevertheless an observant medical staff, who can move freely over the whole of a famine area, will be able to detect quickly any signs of deterioration in the health of the people.

The prevention of epidemics

An adequate supply of sanitary stores, including vaccines, insecticides and disinfectants, should be available, with sufficient reserves kept in medical stores to meet any further emergency. Most epidemic diseases can be readily controlled by prompt action in the first few days after their appearance ; once they are established, control may become impossible before a large toll of mortality has been taken.

The Public Health Service must be maintained and, as far as possible, expanded, even at the expense of the clinical staff. Any breakdown in this service can be the direct cause of innumerable deaths.

The organisation of famine hospitals

Small hospitals widely dispersed amongst the people are more valuable than large institutions. A nearby hospital will help to maintain confidence and so prevent wandering and social disruption. In such hospitals elaborate diagnostic equipment is of secondary importance. Sufficient blankets, kitchen and sanitary equipment, simple drugs and enough staff to allow rapid expansion in an emergency, are essential. Relief workers, if healthy and intelligent, can be rapidly trained to perform hospital duties, even if previously quite inexperienced in hospital work. At Belsen, medical students made excellent workers and their energy, enthusiasm and common sense more than compensated for any deficiencies in technical training. It is the first duty of a medical superintendent to recruit and train a staff sufficiently large to meet any foreseen emergency. In selecting recruits enthusiasm, intelligence and health are the essentials : deficiencies in technical knowledge can rapidly be made good.

Treatment in a famine hospital

The treatment of starvation has been described in Chapter 26. In the early stages rapid recovery frequently follows a few days feeding and attention to minor ailments. If treatment is neglected at this stage the condition of the patient may rapidly deteriorate. Once appetite is lost and strength is so feeble that he cannot support his weight upright, the prognosis is uncertain, and recovery always slow, even with the best medical and nursing care. It is therefore very important to give the best medical care to the minor sick.

Feeding arrangements must be simple and there is no place for elaborate dietary regimens. In a famine hospital the first essential is the preparation of simple, well-cooked meals. The provision of suitable kitchen and dining-room accommodation and equipment may be difficult and—if so—should command the doctors' attention. A large staff of nurses and orderlies are necessary when many patients are too weak to go to the dining halls.

Experience has shown that even a small medical service, if well run, will have a beneficial effect in maintaining public confidence. A shortage of doctors, nurses and orderlies is inevitable and every individual doctor must train his assistants to accept the work delegated to them. His chief task is thus administration and supervision. The ability to foresee needs for simple remedies and equipment is essential, and for success it is necessary to be a master of improvisation.

CONCLUSION

Famine relief inevitably presents many and diverse problems. It is often difficult for a worker on the spot to sort out what is essential from what is only desirable. It is hoped that this chapter will stimulate thought on the principles of relief, for in famine forethought is the best antidote to disaster. An FAO/WHO report (1951) gives some further useful information.

Chapter 54

DIET AND DENTAL DISEASE

THE teeth are a living memorial to the defects of the previous diet. Too often by middle age a few crumbling and unstable tombstones are all that remain to commemorate past errors. This is a misfortune, since there can be no question that good teeth and gums are important for maintaining health. The value of sound dentition in promoting good digestion, and the harm that may come from dental sepsis, have been discussed in Chapter 38. Furthermore it is worth remembering that the appearance of bad teeth, and the fœtor that may come from them, are undesirable for æsthetic reasons.

Two closely associated pathological processes need to be considered : dental caries (decay of the teeth) and periodontal disease of the gums (pyorrhœa alveolaris). Before discussing their causes, it is pertinent to consider their history and distribution among different peoples in relation to dietary habits.

History and geographical distribution

Both caries and periodontal disease occur among people of British ancestry throughout the world and among other people who have adopted their dietary habits. Rickets used to be called ' the English disease,' but caries has at least as much title to that name. A German visitor to the Court of Elizabeth I left a personal impression of the Queen ; he remarked on her hooked nose, narrow hips and bad black teeth ; the latter explained as ' a defect the English seem subject to from their too great use of sugar.' George Washington (a man of impeccable British ancestry) was one of the first ever to wear false teeth.

Although the British have always been prone to bad teeth, the evidence of mediæval graveyards suggests that the standard of dental health was much better a few centuries ago than it was in the nineteenth century. The subject has been excellently reviewed by Drummond and Wilbraham (1939). They concluded that the decline in dental health that took place in the last century was due to the altered eating habits of country people coming into the new industrial towns. The changes which they thought most important were : (*a*) the decline in the consumption of milk, (*b*) the general use of refined sugar which had previously been an aristocratic delicacy and (*c*) the introduction in the 1880's of roller-milled white wheaten flour which was softer and less nutritious than the traditional wholemeal stone-ground wheat (Chapter 17). Certainly by 1900 the general state of dentition in Great Britain was deplorable ; bad teeth was one reason that led to such a high rejection of recruits for the Army at that time.

By contrast, good dentition is the rule in certain primitive (though not necessarily uncivilised) people. The Eskimos have excellent teeth until they forsake their traditional diet (largely composed of raw walrus meat and fish) and begin to buy canned foods at the local trading station (Pedersen, 1947). The Masai in Kenya, who live almost entirely on milk, meat and raw blood, have little caries, as Orr and Gilks (1931) reported. Their neighbours, the Kikuyu, on the other hand, whose diet is rich in carbohydrates and who readily adapt themselves to European dietary habits, are prone to caries. In many underdeveloped countries such foodstuffs as refined wheat flour and sugar and sweetened soft drinks nowadays form a regular part of the diet of the indigenous people, particularly in the towns. The incidence of caries and periodontal disease among the children of such communities, where the facilities for dental care and treatment are still limited, is often very high (Nicol, 1956). Their parents frequently have lost many teeth, a large number of those remaining being loose and embedded in pools of pus.

In France and Norway (Toverud, 1949) the dental health of children actually improved in the Second World War during the German occupation, despite the cruel restriction in food supplies. Sugar and sweets were, of course, almost impossible to obtain ; the people reverted to the traditional short commons of the European peasantry—wholemeal bread and such vegetables as they could grow for themselves. Though the supply of milk for children was appallingly deficient, they nevertheless developed good teeth.

DIET AND DENTAL STRUCTURE

The substance of the teeth is mainly composed of a bone-like material, *dentine*, which is protected on its outer surface by a thin layer of very hard *enamel*. Inside is the soft *pulp cavity*, supplied by a nerve and an arteriole.

The structure of dentine resembles that of bone in that it is composed of a cellular, protein-containing organic matrix in which calcium salts (mainly phosphate) are deposited. But dentine is denser than bone. Whereas bone consists of about 40 per cent. of inorganic salts and 60 per cent. of matrix, dentine contains about 80 per cent. of inorganic salts. Enamel is even more dense, with less than 5 per cent. of matrix which nevertheless plays an essential part in maintaining its structure. Even the enamel surface of a tooth is a living tissue.

The various known factors that may affect the development and subsequent life of the teeth can be divided into (1) systemic factors, mediated through the blood supply, and (2) local factors.

1. Systemic factors

Factors influencing calcification.—The regulating mechanisms controlling the absorption and retention of calcium by the body have been discussed in Chapter 11. Several dietary factors, including the amount of calcium in the food and the supply of vitamin D, determine the inorganic structure of the teeth.

Factors influencing the matrix.—Although these have received scant attention in the past they are probably equally important. They are likely to be the same as those affecting the matrix of the bones. Changes in the bony matrix result in osteoporosis (Chapter 30) which occurs particularly in elderly bedridden patients. It has been suggested that teeth, like bones, may similarly suffer from ' disuse odontoporosis.'

Factors influencing enamel—VITAMIN A.—The cells (ameloblasts) that make the enamel of the teeth have their origin in the primitive epithelial structures of the body. Vitamin A is concerned with the normal structure of epithelium. It is therefore understandable why puppies fed on a diet deficient in this vitamin develop defective enamel. Nevertheless there is no satisfactory evidence that vitamin A deficiency in children is severe enough to affect the development of their teeth. There is no characteristic disorder of the teeth associated with xerophthalmia.

FLUORINE.—The salts present in dentine and enamel normally contain, besides calcium phosphate and bicarbonate, traces of other elements including fluorine.

A concentration of fluorine in drinking water between 0·5 and 1 part per million (p.p.m.) protects against caries ; but if the drinking water in a locality contains more than 2 p.p.m. of fluorine, permanent white flecks are found in the dental enamel of its inhabitants. At higher levels of fluorine (*e.g.* 5 p.p.m.) in the water, every tooth may be affected and the enamel surface is often irregular and stained brown at the gum margins. Such teeth are softer than normal, and yet unusually resistant to dental decay. The presence of abnormal amounts of fluorine has been demonstrated in these teeth, and it is likely that the bactericidal power of this element is the factor that protects them from caries.

Effects of defective structure.—When, during the course of their development in childhood, the teeth lack sufficient calcium and other materials necessary to build a firm dentine and dense enamel, *enamel hypoplasia* results. This is of two kinds.

1. In *G-hypoplasia* (gross hypoplasia) the enamel surface is seen to be deeply pitted. The pitting is often present in a regular line affecting most of the teeth. This hypoplasia can often be ascribed to an illness in early childhood—such as whooping-cough—that prevented an adequate intake of calcium at the time when the permanent teeth were developing.

2. The less familiar kind was first described by Lady May Mellanby and therefore called *M-hypoplasia*. There is a general defect in development of the enamel so that the surface of the tooth, instead of being perfectly smooth and hard, has an irregular ' wash-board ' texture, which is often more easily felt than seen, by running a fine probe over the posterior surface of the tooth. Lady Mellanby, in a long series of investigations, has demonstrated a close association between the incidence

of M-hypoplasia and of caries in London school children (Mellanby & Mellanby, 1954).

2. Local factors

The food that daily comes in contact with the teeth naturally has an effect on their surface structure. Hard, tough foodstuffs might be expected to wear the teeth down, but the teeth of people accustomed to chewing such foods usually show little signs of wear. The cellular matrix in the enamel is able to repair the effects of attrition, provided that it continues to receive an adequate supply of nutrients *via* the blood. Worn or faceted teeth are more often the result of some change in their structure.

Infection.—It is not hard foods that give rise to caries so much as soft ones. Soft foods that need little chewing tend to leave remnants behind in the spaces between the teeth and these remnants are an excellent breeding ground for bacteria. Miller when working in Koch's laboratory in Berlin towards the end of last century drew attention to the fact that bacteria can ferment sugars, producing lactic acid which will dissolve the calcium salts of dental enamel. The organism principally concerned is the *Lactobacillus acidophilus*. In recent years medical scientists have been more preoccupied with the chemical pathology of teeth and so have tended to discount the factor of infection in the causation of dental caries. Now—after more than half a century—the views of Miller are becoming popular once again.

The foods most likely to be responsible for the acid erosion of dental surfaces are soft, sticky carbohydrate-containing foods such as white bread and sweets (candy). Although it has been reported (King *et al.*, 1955) that extra sugar *per se* (taken with the meals in the form of highly soluble sucrose) does not affect the incidence of caries, this does not detract from the possibility that sweets made of sticky and less-soluble glucose, taken between meals, can lodge in the teeth long enough to allow bacteria to produce acids from them and so to cause surface erosion.

Saliva.—Undoubtedly a free flow of saliva is of value in keeping the surface of the teeth clean and free from erosion. When salivary glands are removed for surgical reasons or destroyed by irradiation, severe dental caries quickly follows. It has often been suggested that the composition of the saliva (*e.g.* its buffering power) may also be important, but the evidence is inconclusive.

PERIODONTAL DISEASE OF THE GUMS

Pathology

Healthy gums, like the skin of the hands, have a surprising ability, for a soft tissue, to withstand hard usage. They are covered with a firm epithelium, below which there is dense connective tissue.

When periodontal disease is present, the gum margins fall away from their immediate contact with the teeth and may be withdrawn several millimetres from their original point of attachment. The margin is usually intensely red and inflamed, probably because of the bacteria that inevitably accumulate in the pocket that develops between the tooth and the margin of the gum. Their growth is certainly assisted by accumulations of *tartar*. This material consists of a deposit of calcium salts, mucin and bacteria. The cause of its formation is obscure. The first deposits of tartar begin in the pockets between the teeth and the gums. Indeed it has been argued that if the gums are perfectly healthy and closely applied to the teeth this would not occur. Lack of saliva is certainly not the usual cause. Whatever may be the ætiological relationship between tartar and periodontal disease, the fact remains that they are closely associated. In advanced cases the gingival bone underlying the gums is eroded so that the teeth become loose and ultimately fall out, even though they may be free of caries.

The various factors known to be concerned in the cause and prevention of disease of the gums will now be considered.

Infection.—The relative importance of bacterial infection in the causation of periodontal disease has yet to be determined. It is still possible that one reason why country folk soon after coming to the city often develop periodontal disease is that they are exposed for the first time to new mouth-infecting organisms.

Dietary factors

Ascorbic acid.—Deficiency of this vitamin reduces the ability of connective tissue cells to elaborate their collagenous intercellular substances. The distinctive type of inflammation of the gums (gingivitis) that occurs in scurvy is described in Chapter 31. Scurvy also leads to defective formation of dentine ; the teeth may become loose from lack of the cement that normally holds them to the jaw. In severe periodontal disease the teeth also become loose through erosion of the surrounding bone. It is unlikely, however, that lack of ascorbic acid is usually an important factor in the causation of periodontal disease.

Vitamin A.—Lack of this vitamin causes thickening and desquamation of epithelial surfaces. In puppies at least, this affects the gums, causing an accumulation of desquamated cells in pockets between the gum margin and the teeth. These pockets become a nidus of bacterial infection, so that gingivitis results. Nevertheless it is doubtful if vitamin A deficiency is usually a cause of periodontal disease in man.

Protein.—Up to the present there is no evidence that protein deficiency, or indeed lack of any particular nutrient other than ascorbic acid, has any specific influence in maintaining the health of the gums. Local factors are likely to be more important.

Physical effects.—It is noteworthy that periodontal disease is rare among primitive people who make full use of their teeth. The massaging effect of rough, tough foodstuffs no doubt quickly removes the earliest deposits of tartar. As an instance, children in Jamaica have excellent gums, perhaps because of their habit of chewing pieces of sugar-cane between meals ; the cane, despite its sugar content, seems to keep the teeth and gums healthy by its local abrasive action. Similarly, Eskimo women keep their gums clean and in good health by chewing strands of sealskin which they afterwards use for weaving. Unfortunately chewing-gum is too soft to serve this useful purpose.

Foods that need to be chewed not only massage the gums but perhaps prevent the teeth from developing ' disuse odontoporosis ' (p. 768). It is unlikely, however, that the modern man will ever be persuaded to return to the gross, bone-chewing habits of the Tudor kings. Although Queen Victoria made it respectable to nibble at a pheasant's wing held in the fingers, this was scarcely enough. Consequently the modern man with his polite dietary habits must perforce see his dentist regularly.

The relation between periodontal disease and caries.—Although these two conditions are frequently seen together in the same patient this is not necessarily always the case. For instance, on the island of Tristan da Cunha the inhabitants had remarkably little caries but many have periodontal disease, whereas the Pitcairn Islanders have healthy gums but severe caries. As a rule, however, the accumulation of tartar in the pockets and crevices of unhealthy gums tends to cause erosion of dental enamel, so that periodontal disease may be a subsidiary cause of caries.

THE PRESERVATION OF DENTAL HEALTH

Clearly the relationships between dental disease and dietary defects are not simple. Nevertheless there is enough evidence to state several practical principles for the prevention of dental disease.

1. **Infant nutrition.**—The foundations of the first teeth are laid down before birth. It is therefore most important that proper attention should be paid to the nutrition of the pregnant mother, as described in Chapter 57. For the newborn infant it is necessary to ensure that proper calcification of the teeth and bones continues, as discussed in connection with the prevention of rickets (Chapter 29). A good maternity and child health service is sound prophylaxis against caries in the next generation.

2. **Fluoridation of water supplies.**—There can be no question that insufficient fluorine in the drinking water of a community increases the incidence of dental caries among children (Chapter 12). The public health authorities in over a thousand towns and cities in North America have for years deliberately added fluorine to water supplies deficient in the element and have proved the value of this prophylactic measure. The amounts added have been far below any possible toxic level and only sufficient to bring the total fluorine content of the water to 1 part per million. A most careful appraisal of the American experience was made by an official U.K. Mission (1953), with the result that fluoridation was introduced, on trial, in three localities, Watford, Anglesey and Kilmarnock, in Great Britain. A recent report has shown that fluoridation of water in these localities caused a marked reduction in the caries in the children (p. 189).

Unfortunately further progress has been handicapped by much ill-informed opposition by people emotionally opposed to any tampering with ‘ natural ’ water.

We have no hesitation in stating that where a public water supply is deficient in fluorine, this deficiency should be made good and that this will reduce the incidence of dental disease in children.

3. **Dental services.**—Every well-organised community should provide services whereby the teeth and gums of pre-school children, school children and adolescents are inspected—and if necessary treated—at regular intervals. This should be carried out not only in schools, but also in training colleges and industrial works that employ young people.

Although our knowledge of how to prevent the onset of caries is far from adequate, there can be no question that proper treatment at an early stage will arrest the progress of the disease and prevent the loss of teeth in later life.

4. **Education.**—A good dental service provides opportunities for proper education. In communities where dental disease is common, three points should be stressed. First, that prevention is better than cure ; regular attendance at a dental clinic for a prophylactic inspection will save much future trouble. Secondly, it should be known that the teeth and gums ought to be kept clean at all times. For the modern city dweller the regular use of a toothbrush—properly applied—as soon as possible after meals, should be recommended. Thirdly, it should be stressed that sticky sweets or soft starchy foods between meals are harmful, since they lodge between the teeth and encourage dental decay. The tax on sweets introduced in the 1962 British budget is as logical as taxes on tobacco and alcohol. It may help to reduce excessive consumption.

There can be no doubt that if dentists, doctors, dietitians and school teachers devoted more time to educating young people in the care of their teeth, much dental disease could be avoided.

CHAPTER 55

SIMPLE GOITRE

THE term ‘ goitre ’ is used to denote enlargement of the thyroid gland of whatever kind. ‘ Simple ’ goitre is a generalised enlargement of the gland, without symptoms either of hypothyroidism or hyperthyroidism. It is endemic in many parts of the world and virtually absent in others. Millions of people, in the endemic areas, have some degree of thyroid enlargement. Such goitres may not ordinarily affect health, but they sometimes result in complications which may have serious consequences (p. 779).

There can be no doubt that environmental rather than hereditary factors are responsible for determining the incidence of simple goitre—and especially dietary factors. Since goitre is a world-wide problem, involving questions of diet, it requires consideration in this book.

GEOGRAPHICAL DISTRIBUTION

Before discussing the pathology of simple goitre it is useful first to review its incidence.

The endemic form occurs chiefly in three types of terrain :—

(*a*) In mountainous areas of Europe, Asia, the Americas and Africa, such as the Alps, Himalayas, Andes, Rockies and Cameroon mountains.

(*b*) On alluvial plains that were recently covered by glaciers, such as the area round the Great Lakes of North America and in some areas of New Zealand.

(*c*) In isolated localities where the water in common use is obtained from wells or springs originating in limestone, as in Derbyshire and the Cotswolds in England.

It used to be thought that goitre occurred only in areas remote from the sea. It was even suggested that iodine vapour was carried inland by sea breezes to fertilise the neighbouring land. This idea is now wholly discredited. First, the sea itself contains a very low concentration of iodine ; secondly, edible plants grown near the sea have been found to be no richer in iodine than those grown elsewhere ; thirdly, goitre is quite common in some seaboard regions (*e.g.* South Wales). It is true, however, that sea foods, fish and shellfish, are reliable sources of iodine ; so also is seaweed, from which iodine was first isolated. Carrigeen ‘ moss,’ a seaweed still used as food on the west coast of Scotland, may have unsuspected nutritive value in this regard; also in some parts of the Orient seaweed is used as food.

The endemic form occurs most commonly in remote, backward and often impoverished rural communities with primitive sanitation and water supplies. It is noteworthy that in India goitre is not common in the rice-eating inhabitants of Madras, despite their very low intake of iodine (McCarrison *et al.*, 1927).

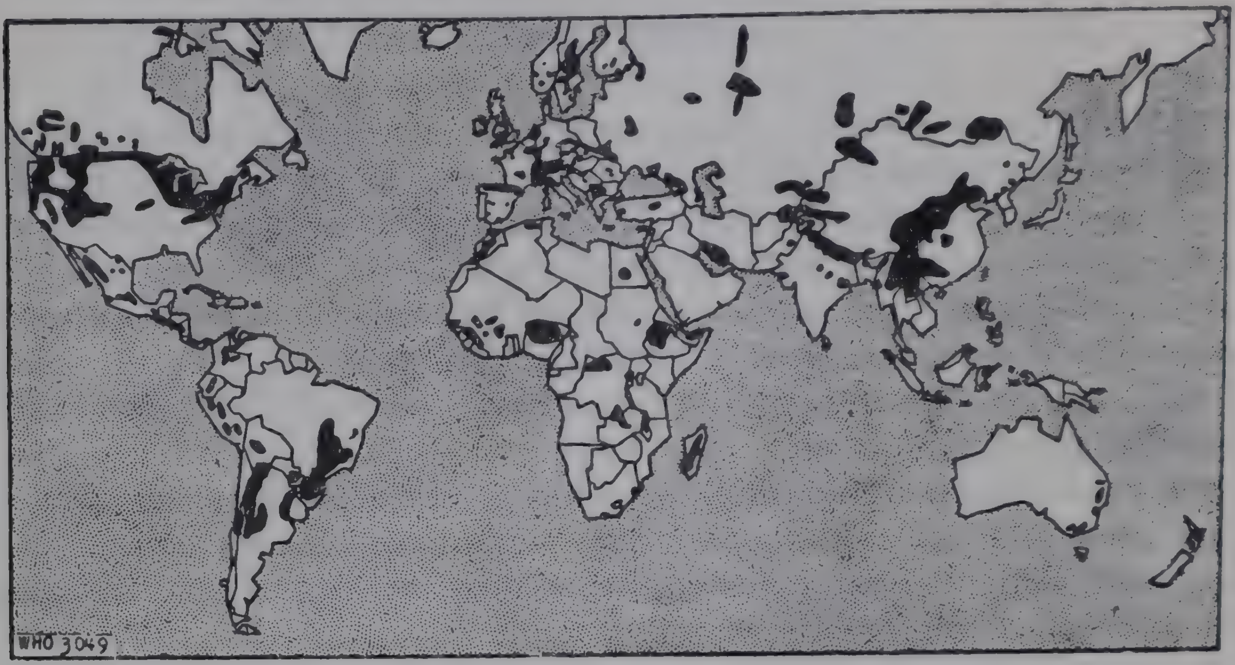

FIG. 55, 1

The world-wide prevalence of endemic goitre has been reviewed by Kelly and Snedden (1958). Its distribution is roughly shown in the map (Fig. 55, 1).

The sporadic form of simple goitre may occur in a person born and raised in regions far removed from areas where goitre is endemic. Its cause is uncertain; it may be that the various ætiological factors mentioned below affect them at a level that produces no disorder in the great majority of their neighbours.

PATHOLOGY

Morbid anatomy.—The normal gland is composed of a multitude of follicles filled with acellular, eosin-staining colloid. This material consists of thyroglobulin, an iodine-containing protein, from which the normal hormonal secretions of the gland are derived. Each follicle is surrounded by a layer of cells which synthesise the hormones.

The enlargement of the gland in simple goitre has been attributed by some authors to overgrowth (hyperplasia) of the cells lining the follicles and by others to an excess of colloid. Both explanations are probably correct; the cellular hyperplasia and accumulation of colloid in the iodine-deficient gland can perhaps be compared with the overgrowth of osteoblasts and accumulation of osteoid tissue that take place as a result of lack of calcium at the growing points of the bones in rickets. Alternatively, there may be a variety of pathological processes contributing to the production of a simple goitre as suggested below, providing no uniform picture for the morbid histologist.

Colloid goitre.—Simple goitres that have been present for years may become very large and interfere with breathing. However, goitres which appear superficially to be small may cause serious respiratory embarrassment and other pressure effects by retrosternal growth. To most people a prominent goitre is unsightly, but in certain areas of Africa where the condition is endemic such tumours are considered a sign of beauty (Plate XXX). The microscopic appearance of these large goitres is generally that of a massive accumulation of colloid in thin-walled follicles.

Nodular goitre.—In long-standing cases of simple goitre another change sometimes takes place: the development of nodules which are localised areas of cellular proliferation within the gland. Similar nodules sometimes occur—perhaps for other reasons—in people who have never lived in a goitre area. Hyperthyroidism and malignant changes occur in rare instances in patients with nodular goitre.

Chemical pathology.—The importance of iodine in relation to the thyroid gland has been discussed in Chapter 12. The normal thyroid gland contains a total of about 8 mg. of iodine. In simple goitre this amount may be reduced to about 1 mg., even though the gland is larger. There can be little doubt that the essential cause of simple goitre is an inability of the thyroid gland to make sufficient thyroxine, which contains 64 per cent. of iodine.

Simple goitre arises most commonly at those periods in life when there is a general alteration in hormonal activity in the body, notably during adolescence and pregnancy. In endemic areas if the incidence is low, only the women have goitres; but if the incidence is high, the men may be almost equally affected.

Marine in the U.S.A. was at great pains to prove that the cause of simple goitre was a deficient intake of iodine. He carried out experiments on trout in which the addition of iodine to the water prevented enlargement of the thyroid gland. He also was able to prevent the appearance of goitre in people living in an endemic area by the use of iodised salt. The evidence that he collected (Marine, 1924) is worthy of study. But, as so often happens in the investigation of an obscure disease, a problem that at first seems capable of simple solution soon becomes difficult again. Nevertheless the work of Marine and his colleagues served a most useful purpose at the time; it focused attention on the iodine intake and proved that goitre is essentially a deficiency disease and not the result of bacterial infection. It also showed the way to its prevention.

ÆTIOLOGY

Iodine deficiency.—Were goitre a simple matter of iodine deficiency, there would be no further need for discussion. In fact, however, few other diseases in recent years have provoked such a spate of articles, official reports and editorials in learned journals. The monograph of Kelly and Snedden (1958) lists 939 references. It is beyond the scope of this book to review all this literature, but the references cited in the following pages provide bibliographies for readers especially interested in the problem.

The chief protagonist to the belief that simple goitre results from a multitude of causes including iodine deficiency has been Sir Robert McCarrison. Beginning in 1905 with an Irish distrust for simple explanations, for 30 years he investigated goitre in India by combining the methods of human ecology and laboratory experiment. Without denying the value of iodine supplements in the prevention of goitre he thought, nevertheless, that the cause of the disorder was more complicated. In Gilgit, in the foothills of the Himalayas, there were eight villages in series, each deriving its water supply from the same stream—progressively contaminated with sewage—from the village above. The incidence of goitre was highest in the lowest village. But a neighbouring village was entirely free from goitre ; this village had an independent water supply from a spring. McCarrison (1908*a*, 1908*b*) filtered off the solid matter from the water coming from the goitrous villages and he himself and some army volunteers drank it. A third of them soon developed goitre, whereas others (controls) drinking the water after it had been boiled failed to do so. McCarrison's extensive publications on goitre have been collected and edited by Sinclair (1953).

The iodine deficiency theory of goitre has been criticised by Greenwald (1955) on the grounds (*inter alia*) that much of the early work purporting to show that the iodine content of the food in goitrous areas was low, was based on methods that were inadequate to measure accurately the small amounts of iodine involved. Also, the clinical methods used to estimate the degree of enlargement of the thyroid gland in people receiving, or not receiving, additional iodine were notoriously subjective, depending on the observation or enthusiasm of the examining doctor. Furthermore, the statistical treatment of the data rarely conformed to modern standards. Many of these criticisms have been answered by an admirably conducted experiment by Scrimshaw and his colleagues (1953) demonstrating the value of iodine supplementation in Guatemala.

Dietary factors interfering with the utilisation of iodine

Goitrogenic substances in food.—In 1928 Chesney and his colleagues (1928) at Johns Hopkins Hospital made the chance observation that rabbits raised in the laboratory for the study of syphilis and fed largely on cabbage developed goitres. This observation was followed up by Sir Charles Hercus and his colleagues in New Zealand. They established the goitrogenic properties of cabbage, turnips and particularly the seeds of cabbage, mustard and rape (Hercus & Purves, 1936). From this came Kennedy's (1942) suggestion that the responsible substance in these vegetables is thiourea. This led Astwood (1943) at Harvard to try thiourea and thiouracil in the treatment of hyperthyroidism, with such success that he thus paved the way to the modern medical treatment of hyperthyroidism. Subsequently Astwood and his colleagues (Greer *et al.*, 1949) isolated and identified the chemical nature of thio-oxazolidine, the goitrogenic substance present in rape seed. This identification of a natural inhibitor of the thyroid gland opened up a whole new concept of positive dietary agents in the causation of disease, by contrast with the idea of deficiencies.

For instance the incidence of goitre among children in Tasmania was increasing despite the general use of iodised salt. The apparent explanation is that there has been a simultaneous effort to increase the consumption of milk. ‘ Many-headed kale ’ has been introduced to feed the expanding dairy herds. The milk of the cows seems to carry with it the goitrogens derived from the kale (Clements, 1955). Several other foods besides the *Brassicæ*, such as groundnuts and soya bean, also have goitrogenic properties.

Hardness of drinking water.—Water is said to be ‘ hard ’ when it contains sufficient salts of calcium or magnesium to precipitate as insoluble curds the fatty acids present in washing soap. When French physicians (then the leading authorities) were first invited to investigate the high incidence of goitre in Colombia, South America, Boussingault (1831) suggested that the hardness of the water was the principal cause. McCarrison also found evidence that the hardness of the water was a factor determining the incidence of goitre in the Himalayas. Despite a subsequent tendency to discount these observations, there can be no doubt now that hard water is sometimes goitrogenic. As an example, two areas in Scotland may be compared ; in Langholm, Dumfriesshire, the water is very hard and goitre common, despite a fair supply of iodine in it (1·6 μg./*l.*) (Medical Research Council, 1948). In Fort William, on the other hand, goitre is rare although the water which is soft contains only half as much iodine. Indeed, the general rarity of goitre in the Highlands of Scotland may well be due to the softness of the water. The ample rainfall in the Highlands provides abundant surface water which, seeping first through peat bogs, acquires enough acids to precipitate any salts of calcium and magnesium that may lie on the surface.

It is interesting to reflect that the surface water that supplies Glasgow has for years been deliberately hardened by the addition of limestone, to prevent lead poisoning caused by the effects of acid peat-water on lead pipes in the old tenements. No one has yet complained that the water supply thus artificially treated might be a cause of goitre, though violent protests have lately been lodged against the further addition of fluorides (Chapter 12).

In the chief goitre areas of Great Britain (*e.g.* Derbyshire and the Cotswolds) the water supplies often come from deep wells or springs flowing from limestone caves where it has lain for long periods in contact with soluble mineral salts. Many of the suburbs of London are supplied with very hard water which comes from artesian wells forced up from a cup-shaped bed of subterranean chalk. This water, made hard by almost pure calcium carbonate derived from chalk, does not appear to be particularly goitrogenic. This gives rise to the suspicion that it is not so much the calcium in hard water that is goitrogenic, but other elements that are dissolved with it. Fluorine has been suggested as the element that might be concerned (Galleti & Joyet, 1958). Magnesium is another possibility that has not yet been adequately investigated.

Perhaps the real deciding factor is the balance between the amount of iodine provided by the water, set against the amount of dissolved salts that tend to inhibit its effects. Taylor (1954) has shown that rats on a marginal iodine intake develop goitre if their diet is ' enriched ' with 2 per cent. calcium carbonate. Just how dissolved salts affect the utilisation of iodine has yet to be determined ; they may hinder its absorption, increase its excretion, or interfere with the synthesis of thyroid hormone.

Dirty water.—Goitre is chiefly a disorder of primitive country folk tending herds of sheep or cattle on mountains or on alluvial plains left by glaciers. Their water supplies are often dirty and contaminated with human or animal excreta, as Marine himself confirmed. Later he tended to discount this observation in the growing certainty that iodine deficiency was the only important issue. But McCarrison continued to contend the validity of his own observations. Although this aspect of the subject has been almost forgotten until recently, it still seems likely that water contaminated by animal or human fæces contains some organic substance that is goitrogenic. The idea is at least venerable since the Chinese, the Greeks and the Romans all attributed goitre to bad water. So did the inhabitants of Central Africa interviewed by David Livingstone.

Stress.—The activity of the thyroid gland is regulated by the anterior pituitary gland through the thyrotrophic hormone. It is known that stressful situations of all kinds increase the activity of the pituitary gland. At one time it was thought that hyperthyroidism (Graves' disease) was the result of stress ; recent evidence has tended to discount this possibility and in doing so has distracted attention from the possibility that stress may affect the thyroid in a different way, by producing simple goitre.

Epidemics of goitre have been described in people surviving in difficult circumstances. Captain Cook observed it in his crew during his long voyage to Australia in 1772. The increased incidence of simple goitre in Brussels following the German invasion has been recorded by Bastenie (1947). Although this may have been due in part to the large enforced consumption of *Brassicæ* vegetables, the influence of psychological stress may also have played a part. An increase in the size of the thyroid has been reported in a variety of fevers.

Pregnancy.—The raised level of iodine in the blood in pregnancy and the relatively high iodine content of the ovaries both suggest that iodine is particularly important in the physiology of reproduction. This may explain why goitre sometimes develops during pregnancy and at puberty.

COMMENT

The problem of goitre may be summarised thus: the thyroid gland needs an adequate supply of iodine for the synthesis of its hormone. With a good dietary intake of iodine there is no difficulty, but when supplies of this element are marginal, a variety of conditioning factors may intrude to interfere with its utilisation.

Clinical effects and complications

In the great majority of cases of simple goitre there are no clinical manifestations due to hypofunction or hyperfunction of the thyroid gland. Simple colloid goitre may require surgical treatment either for æsthetic reasons or because of pressure effects on the adjacent structures. The following complications occur rarely: (1) hypothyroidism, (2) hyperthyroidism, (3) cretinism, and (4) deaf-mutism. Such complications are more likely to be encountered in regions where endemic goitre is prevalent. These undesirable clinical effects and complications can be greatly reduced by the appropriate prophylactic measures described below.

Treatment

Simple goitre responds well to small therapeutic doses of iodine, but by the time colloid accumulation or nodule formation has developed, there is usually no response. Proper management therefore lies in prevention rather than cure.

Prevention

The existing evidence is wholly in favour of the value of iodine supplementation as the most simple means of eradicating endemic goitre and its complications. The Study Group on Endemic Goitre of WHO (1953) expressed the opinion that "when iodine prophylaxis has been introduced and efficiently carried out, endemic goitre is practically abolished." The evidence was previously reviewed by The Goitre Sub-Committee of the Medical Research Council (Murray *et al.*, 1948) who recommended that salt sold in Great Britain should be iodised. If both table and cooking salt were to receive the addition, 1 part of potassium iodide in each 100,000 parts of sodium chloride was recommended. Assuming an average daily intake of 10 g. NaCl, this would provide daily 0·1 mg. KI or 75 μg. of iodine. If table salt only is iodised (of which the average daily intake is about 3 g./day) then the level should be raised to 1 part KI in 30,000 to 50,000 parts NaCl. It should be noted that these recommended amounts are only one-tenth of the extra iodine provided in salt in the U.S.A. and about a fifth of the supplement in New Zealand. The experience in these and other countries, extending over more than 25 years, can leave no doubt that the addition of iodine to salt in these amounts has had nothing but beneficial consequences.

Nine countries in Latin America have reported the passing of legislation requiring the iodisation of salt, the recommended levels varying from 1 part iodine in 20,000 parts salt to 1 part iodine in 10,000 parts salt, consideration being given to the average per caput salt consumption and the possible prevalence of goitrogenic factors (FAO/WHO, 1955, 1958*b*). On account of its stability potassium iodate is preferable to potassium iodide for the iodisation of the crude moist salt consumed in many countries. The decision of UNICEF to provide equipment and supplies for salt iodisation is enabling additional countries to reduce the incidence of goitre in their populations.

The British Government has failed to implement the recommendations of the Medical Research Council in regard to the iodisation of salt. When this failure was pointed out in the House of Commons it was stated that there were difficulties of a technical nature. It is surely not beyond the technical skill of salt manufacturers in Great Britain to carry out a procedure that has been in regular operation in Switzerland for over 30 years and subsequently adopted by other progressive countries, such as New Zealand, Australia and the U.S.A.

CHAPTER 56

NUTRITION AND INFECTION

IN considering the relation between nutrition and infection it is necessary to keep in mind three distinct problems :—

1. The role of nutrition in protecting the body against invasion by infecting organisms (*i.e. susceptibility* to infection).
2. The role of nutrition in enabling the body to overcome an infection once established (*i.e. resistance* to infection already acquired).
3. The influence of infectious diseases on food intake and food production and so on the future state of nutrition.

The belief that nutrition has an effect upon susceptibility and resistance to infection seems logical and reasonable. The recorded history of mankind demonstrates repeatedly the close association between war, pestilence, famine and death. St John (Revelation vi, 2) describes this association in his allegory of the Four Horsemen of the Apocalypse. Unfortunately, however, it must be admitted that the factual evidence supporting a causal relationship between poor diets and susceptibility to infectious diseases is far from satisfactory. However, there is no doubt that malnourished patients often have a low resistance to an infection once it is established. The role of infectious diseases in precipitating nutritional disorders, such as kwashiorkor, beriberi and keratomalacia, by increasing the needs for essential nutrients is now realised to be very important. Before considering these problems a brief summary of the defences of the body against infections is given.

THE DEFENCES OF THE BODY AGAINST INFECTION

There are four main lines of defence against infection.

The skin and mucous membranes.—These are the natural barriers that restrict the entrance of organisms into the tissues of the body. They include the skin, the cornea of the eye and the epithelial linings of the respiratory, gastrointestinal and genito-urinary tracts. The integrity of these barriers naturally depends on the maintenance of a healthy and unbroken surface. Any dietary deficiency that will vitiate the health of epithelial cells and restrict their powers of recovery from normal wear and tear might be expected to facilitate invasion by infective organisms.

A further defence is provided by the protective secretions with which many epithelial surfaces are bathed. Thus the sebum of the skin, the acid secretion of the stomach and the lysozyme in the tears that moisten the eye, all have bacteriocidal properties. Any dietary deficiency that leads to a lessened flow of these secretions might be expected to increase the liability to infection.

Once the invading organism has gained a foothold within the body it then encounters the second line of defence which includes :

Phagocytes.—The polymorphonuclear white corpuscles of the blood and the sedentary cells of the reticulo-endothelial system (located particularly in the liver and spleen) are able to ingest bacteria and remove them from the circulation.

Antibodies.—These protect the body against bacterial or viral invaders by combining with the proteins of the infecting microbes, interfering with their metabolism, causing them to clump together or die, and neutralising their toxic products. These antibodies circulate in the blood, and are found in the gamma globulin fraction of the plasma proteins. They are also attached to cells, notably lymphocytes, plasma cells and the cells of the reticulo-endothelial system ; the last named are fixed in strategic positions where blood-borne invading organisms are likely to come in contact with them. Antibodies are either present in the body at birth, obtained in infancy from the mother's milk, or acquired as a result of subsequent exposure to infection. The first milk (colostrum) is particularly rich in antibodies.

General systemic responses.—The body often reacts to infection by developing fever. The raised temperature indicates an increase of metabolic activity and may sometimes, in itself, create an environment unfavourable to the invading organisms. Starving people rarely develop fever to the same degree as healthy people ; indeed it is the common experience in times of famine to find at autopsy extensive tuberculosis that was unsuspected during life because the patient was afebrile. Other general reactions to infection include increased activity of the adrenal cortex, with reduction in its ascorbic acid content. Exhaustion of the gland following hyperactivity may play an important part in determining the outcome of attacks of cholera and other severe diarrhœal diseases which may cause profound disturbances of the electrolyte balance of the body. The possible effects of nutritional failure on these general metabolic responses to infection have not yet been fully investigated. However, Lurie and Jackson (1962) have shown that adrenal cortical activity may be well maintained in kwashiorkor.

FEVERS, POVERTY AND POOR NUTRITION

It is a familiar fact that infections and infestations are frequently associated with poverty and the lack of sufficient food. In famines (Chapter 53), outbreaks of diseases such as typhus, relapsing fever, smallpox and cholera have been common. The great tropical diseases, especially malaria and dysentery, and infections with hookworms and other intestinal parasites, are most prevalent amongst the poverty-stricken in underdeveloped countries. Fifty years ago in the cities of Europe fatal respiratory infections were common in poor children with rickets in the overcrowded slums. Rheumatic fever was more frequently found in the children of the poor than of the well-to-do. Wherever in the world there has been hunger and poverty, victims of pulmonary tuberculosis have been numerous. Hence it was natural to believe that an insufficiency of suitable foods might increase susceptibility to infectious diseases.

However, poverty is also associated with inadequate houses, overcrowding and insufficient sanitary services. Overcrowding facilitates the passage of micro-organisms from person to person (cross-infection). This is so whether a disease is spread as an air-borne infection or by food or water, or transmitted by insects.

NUTRITION AND SUSCEPTIBILITY TO INFECTION

Whereas the relationship between poverty and infectious diseases is well established, the evidence that dietary deficiencies are important factors in protecting the body against infections is confusing and difficult to interpret. This is well illustrated by numerous studies of the effects of different diets on laboratory infections in experimental animals.

Animal experiments

Most bacteriologists would agree that the previous diet of an experimental animal in general makes little difference to its susceptibility to infection. Unless the diet has been grossly defective either in quantity or quality for a long time, response to experimental infection is unaltered. It is obvious that the protective mechanisms against infection, described on page 781, must be built up and maintained by material derived from the diet. So important are these mechanisms that they appear to have a high priority over others for the supply of essential nutrients. Yet there are many experiments in which it has been unequivocally shown that a poor diet has increased the susceptibility of laboratory animals to an infection, owing to a failure of one or other of these protective mechanisms. The evidence has been summarised and reviewed by Schneider (1946), Howie (1949) and Scrimshaw *et al.* (1959).

These conflicting observations become less difficult to understand if the extraordinary complexity of the chemical relationship between the metabolism of the host and the parasite is appreciated. Even in well-fed laboratory animals the susceptibility to many infectious diseases varies greatly from individual to individual. It is not surprising therefore that in animals lacking in essential nutrients, the complex barrier against infective agents should sometimes break down. This is most likely to occur if there is a lack of protein, the vitamin B group, ascorbic acid or vitamin A in the tissues.

In general these animal experiments lend no support for the view which has sometimes been expressed that susceptibility to infection is increased by the consumption by man of diets, the contents of which are only moderately below the physiological standards discussed in Part I and summarised in Chapter 15. However, serious dietary deficiencies might be expected to lower susceptibility to pathogenic organisms in some individuals.

Observations of human epidemics.—Many times in history infections have spread like wildfire amongst men and women stricken with poverty. This is usually because the insanitary state of their environment has provided ideal circumstances for the pathogenic organs to multiply and to pass easily from one host to another. Opportunities to study infectious diseases in a malnourished community living under good sanitary conditions seldom arise.

PULMONARY TUBERCULOSIS is an infectious disease which has hitherto been closely associated with poverty. It is widely believed that malnutrition increases susceptibility. In the first edition of this book instances were given in which the deaths from tuberculosis increased when nutritional standards fell, but without any obvious corresponding decline in their general hygiene. However, the increased number of deaths might have been due to a lowered resistance to the disease amongst patients previously infected rather than to increased numbers of new patients.

Recent observations in Madras amongst a poor urban population living in very poor houses on deficient diets have a bearing on the problem. A team under the direction of Dr Fox (Andrews *et al.*, 1960 ; Fox, 1962) have shown that the disease can be arrested and its spread from ' open ' cases to their families and other close contacts can be controlled if the infection is adequately treated with chemotherapeutic drugs. In Madras this was found to be effective without the necessity of isolating the patients in sanatoria and with no change in the poor diet, housing and other hygienic circumstances of the community.

INFECTIOUS DISEASES IN EUROPE IN 1939-45.—Although there was a marked increase in tuberculosis during the Second World War, in general the widespread scarcity of food was not associated with epidemics of infectious diseases. In Greece in 1942 and in Holland in 1944-45 there were famine conditions. After the war in Germany there was a marked deterioration in the available food supplies. Yet in none of these countries did epidemics of common infectious diseases arise. The unsatisfactory food intakes did not lead to outbreaks of diseases such as influenza, meningitis and diphtheria.

INFECTIOUS DISEASE IN WELL-NOURISHED PEOPLE.—It is well known that good nutrition does not necessarily protect against infection. Fit and healthy young men and women frequently contract typhus, malaria, smallpox, cholera, infective hepatitis, poliomyelitis, pneumonia and other infections. This is particularly striking when their duties as doctors, nurses, soldiers or missionaries take them into areas where an epidemic is present. They are also susceptible to sporadic infections in the course of their ordinary work. Good nutrition provides no safeguard against an infectious disease.

NUTRITION AND IMMUNITY.—Protective immunity may be obtained in many ways. Antibodies may be acquired direct from the mother either through the placenta or in the colostrum. They may be built up by repeated exposure to small doses of infecting organisms or by protective inoculations. Undernourished slum dwellers may indeed be relatively unsusceptible to certain infections, *e.g.* infective hepatitis and poliomyelitis, as a result of such frequent exposure.

Many studies on men have shown that even severe nutritional failure may not substantially alter the response to immunising antigens (Balch, 1950 ; Gell, 1951 ; Larsen & Tomlinson, 1952). In tropical countries where malnutrition and chronic infections and infestations so frequently co-exist, the deficiency of protein in the diet may lead to a marked fall in the level of albumin in the plasma, while the level of gamma globulin, which includes the antibodies in the plasma, remains high.

CONCLUSION.—It is impossible to provide a concise answer to the first problem posed on page 781. However, it may be stated that a poor diet does not necessarily reduce the efficiency of the body's protective mechanisms against invasion by micro-organisms and so lead to increased susceptibility to infections. Poverty is closely associated with infectious diseases because overcrowding and the poor sanitary services greatly increase the risks of cross-infection. These factors, together with a low level of natural or acquired immunity, appear to be usually more important than a lack of sufficient suitable foods in causing the spread of infectious diseases in man.

NUTRITION AND ESTABLISHED INFECTION

Fortunately the answer to our second problem is easy. There can be no doubt that the previous state of nutrition may be of great importance in determining the result of an infection. There are many clinical and epidemiological observations to support this.

Patients die of infectious diseases because they are unable to withstand the toxic effects produced by the micro-organisms. Toxæmia affects all the organs of the body, but the effects on the heart, the liver and the kidneys are the most important in causing death. In severely malnourished patients the tissues have an impaired ability to withstand toxæmia. A moderately severe attack of pneumonia, dysentery or indeed of any infectious disease, which is easily survived by a healthy well-nourished patient, may be fatal in another who is debilitated and emaciated. Widespread malnutrition contributes largely to the many deaths from infectious diseases in underdeveloped countries. In prosperous countries, good nutrition together with specific antibiotics and chemotherapy enable children and young people to overcome easily most infections which they may chance to contract. In such countries infectious diseases produce a very small proportion of deaths in the young. In North America and Western Europe far more people under 40 die from violent accidents than from all the infectious diseases put together.

INFLUENCE OF INFECTIONS ON NUTRITION

Perhaps more important than the effect of malnutrition in predisposing to infection is the opposite effect—that of infection on nutrition. This can happen in two ways. First, infectious diseases contribute to poverty by reducing the working capacity of individuals. This is best illustrated by the most important chronic disease in the world—malaria. The peasant farmer afflicted with it has an attack of fever when the rains come, and so cannot sow his seed at the right time. His family suffer the next winter from his incapacity, and nutritional troubles result. In a more general way, whenever the breadwinner is struck down by a prolonged infection such as tuberculosis, leprosy, relapsing fever or yaws, nutritional failure is likely to affect his dependants.

Secondly, infectious diseases increase metabolism and the rate of breakdown of the tissues. This creates a need for extra nutrients ; if these are not provided by the diet, nutritional disorders may result. In infancy and early childhood a single acute infectious illness may have a decisive effect on the nutritional health, and indeed on the whole future of the child. The subnutrition brought about by the repeated vomiting of whooping-cough is familiar in Western medical practice. In the tropics, as Dr Cicely Williams has rightly emphasised, one acute episode of infectious food poisoning in an infant weaned on a diet that is already barely adequate is often fatal. An attack of measles frequently determines the onset of kwashiorkor and may suffice to tip the scale against the chances of survival for an infant or toddler struggling to make headway on a poor selection of foods. Oomen (1958) has emphasised that blindness in children caused by keratomalacia is closely associated with recurrent respiratory infections and frequently follows an attack of bronchopneumonia. Dysentery and diarrhœa were recognised as antecedents of acute beriberi in adults living on deficient diets in Japanese prison camps (Smith & Woodruff, 1951).

GENERAL CONCLUSION

Fortunately the uncertainties of the precise relation of nutrition to infection do no affect public health policy. In highly developed countries, in which severe malnutrition is very uncommon, resistance to infection or recovery from infection is probably little influenced by nutritional and dietetic factors ; in underdeveloped countries, on the other hand, where malnutrition is common and often severe, the nutritional factors are of great importance in both the prevention and the treatment of infections. Much practical experience has shown that one-sided public health programmes, aimed solely at improving diets or eradicating a single infectious disease, are relatively unsuccessful in raising the health of a community. This can best be improved by an attack on a broad front against *all* the factors that contribute to disease. Public health programmes must be well balanced and the activities of individual health workers integrated. Isolated programmes may do more harm than good by diverting money and distracting attention from other more important problems. Nutrition workers must always be in active collaboration with those whose duty it is to control infectious diseases and must make themselves acquainted with the problems and difficulties of other health workers. Similarly all the staff of a public health department, especially those concerned with the control of infectious diseases, must appreciate the ill-effects of a poor diet on health and know something of the methods available for improving the nutrition of a community.

CHAPTER 57

PREGNANCY, LACTATION AND CHILDHOOD

PREGNANCY

DESPITE our ignorance of many aspects of nutrition in relation to pregnancy and lactation, there is much sound empirical knowledge gained in general medical practice and also supported by a large scientific literature (Garry & Wood, 1945-46 ; Josey, 1945 ; British Nutrition Society, 1957) in favour of the view that the expectant mother needs a good mixed diet. When assessing the relation of diet to pregnancy the following problems require consideration :—

1. What is the effect of diet on fertility ?
2. What is the effect on the outcome of pregnancy of the diet eaten in the years prior to a woman becoming pregnant ?
3. What is the effect on the outcome of pregnancy of the diet eaten during pregnancy ?

Diet and Fertility

The very high birth-rate in poor women in Asia, Africa and other underdeveloped countries in which the diet is notoriously defective in many nutrients, suggests that it is very unlikely that undernutrition or malnutrition plays a significant role in fertility.

During the occupation of the Colony of Singapore by the Japanese in the Second World War and for some time thereafter, food was very scarce and there was also a great increase in price. Many poor pregnant women were severely undernourished and malnourished. Millis (1952) made a detailed study of the problems of fertility and pregnancy in relation to nutrition in Singapore. Despite the poor nutrition of large numbers of pregnant women (Chinese, Malays and Indians), she found no evidence that fertility was impaired. The pre-war and immediate post-war figures for the birth-rate were approximately the same, both being between 45 and 50 per 1000 of the population.

In prosperous countries in Europe and North America, the much lower birth-rates are not due to reduced fertility consequent on overnutrition, but to the knowledge of methods for the prevention of conception, so that family planning can be carried out according to the wishes of the parents. There have been reports of reduced conception rates in Holland in 1944 when there was an acute food shortage for six months, and in Russia during the siege of Leningrad in 1942. The dietary deficiencies and emotional stresses were greater and more prolonged in the siege of

Leningrad than in Holland. It is probable that the amenorrhœa which occurred so frequently in Dutch and Russian women during these times of stress was due more to psychological and physical causes than to nutritional deficiency.

Diet prior to pregnancy

The likelihood of a normal labour occurring is undoubtedly better in women brought up in good circumstances, who have eaten a satisfactory diet from birth to maturity, who have received good medical care and who continue to have these advantages during pregnancy, than in women of the poorer socio-economic classes. This is not surprising since, in Britain at least, the size of the pelvis is closely correlated with height, and in well-nourished women the shape of the pelvic brim is round. In women who have had rickets in infancy the pelvic brim may be very much flattened and even kidney shaped owing to the extent of the projection of the promontory of the sacrum downwards. Such severe deformities of the brim are rare nowadays, but flattening of the posterior segment of the brim is still found in the short stunted women who are seen in considerable numbers in our large industrial centres. Other factors influencing a satisfactory outcome of pregnancy are fœtal size and presentation. The introduction of antibiotics and better hygiene, housing and general medical care, all play a part in helping to produce a successful birth. It is therefore reasonable to believe that the outcome of pregnancy may be influenced more by the diet partaken prior to conception and by the factors mentioned above, than by the actual diet eaten during pregnancy.

Diet during pregnancy

BIRTH WEIGHT OF INFANTS.—The diet of pregnant women of the upper socio-economic class contains more calories, more protein, more calcium and more vitamins than the diet of women in the lower socio-economic class (Thomson, 1958). The average birth weight of full-term babies and the premature birth-rate of women of the former class are superior to those in the lower socio-economic class. There is good statistical evidence to show that a high calorie intake during pregnancy is associated with a birth weight which is above the average (Thomson, 1959). Whereas the average birth weight of infants of mothers in South India from a high socio-economic group was 3·18 kg., the average weight of infants from a low socio-economic group was 2·78 kg. (Venkatachalam, 1962).

During periods of *severe* malnutrition the birth weight falls. In contrast to the unchanged fertility rate, Millis (1952) found that the average birth weights of Indian and Chinese babies in Singapore was significantly lower in 1947 than in 1950, when the nutritional situation had considerably improved but was still far from satisfactory.

At various periods between 1940 and 1945 in Holland, France, Austria, Germany and Russia, there was a grave shortage of food. Ample evidence has been obtained in these countries to establish the fact that when the mothers were *severely* undernourished there was a decrease in the birth weight of their infants and that this could be correlated with the degree of undernourishment.

WEIGHT OF PREGNANT WOMEN.—Some increase in body weight in addition to the weight of the fœtus, the placenta and the enlarged uterus, is normal. In a study of normal primigravidæ in Aberdeen (Thomson & Hytten, 1960) the average gain in weight during pregnancy was 27·5 lb. (12·5 kg.). Of this total, 11 lb. (5 kg.) can be accounted for by the enlarged uterus and its contents, and about 7·5 lb. (3·4 kg.) by an increase in plasma volume and extracellular fluid, which is lost soon after delivery. This leaves 9 lb. (4·1 kg.) which may perhaps be regarded as an extra store (probably mostly as fat) for use during lactation. A gain in weight of about 9 lb. (4·1 kg.) in the first 20 weeks of pregnancy and thereafter a little less than 1 lb. (0·5 kg.) per week can be considered satisfactory. These are average figures and wide variations from them are compatible with health. There is a good correlation between calorie intake and the amount of weight gained by a mother during pregnancy. There is evidence to support the view that when obesity is present pregnancy is more likely to be attended by essential hypertension, pre-eclampsia and other undesirable complications. Emerson (1962) reviews the literature and gives supporting data for this concept from his studies of 1145 cases. The relationship of obesity to the toxæmias of pregnancy is probably indirect. It is well recognised that the liability to essential hypertension is increased by obesity, and that pre-eclampsia is more likely to develop in hypertensive pregnant women. Thomson and Billewicz (1957) found that an average gain in weight of a little less than 1 lb. per week during the second half of pregnancy is associated with the lowest overall rates for pre-eclampsiā, prematurity and perinatal mortality. With higher rates of gain, the chances of the mother developing pre-eclampsia are increased, whereas with lower rates there is an increase of prematurity.

Many clinicians believe that pre-eclampsia may be prevented if women are not allowed to gain weight excessively during pregnancy. The evidence in favour of this view is not entirely convincing. Every experienced obstetrician has had under his charge many overweight pregnant women who never developed pre-eclampsia or eclampsia, and others below standard weight who developed the disease. At the Seventh International Conference of the International Society of Geographical Pathology held in London in 1960, a symposium was devoted to the ætiology and incidence of pre-eclampsia and eclampsia in many countries differing widely in their socio-economic and nutritional standards, *e.g.* Great Britain, Australia, Switzerland, Nigeria, Japan and others. The conclusion reached (Doll & Hanington, 1961) was as follows : " The response of the cardiovascular system to pregnancy has no obvious relation to diet and, in particular, to its protein content." According to Kellar (1962) the incidence of pre-eclampsia is much the same, about 5 per cent., in most North American and European clinics. In Great Britain dietary surveys during the seventh month of pregnancy have failed to show any qualitative differences in food intake between primigravidæ who do and those who do not subsequently develop pre-eclampsia (Thomson, 1959). Accordingly, at the time of writing, it can be said that satisfactory proof is lacking that either undernutrition or overnutrition is the primary cause of the toxæmias of pregnancy.

It may be more important to discourage women from eating excessively during pregnancy with a view to preventing obesity. Only about half the normal weight gained by a pregnant woman is due to the growth of the products of conception, and an increase of up to 9 lb. (4·1 kg.) of body fat is physiological (see above). If more fat is laid down and if this fat does not disappear during lactation, it will lead to obesity. This may well account for the fact that pregnancy so often marks the beginning of obesity in women.

An excessive gain of weight during the last few weeks of pregnancy is more likely to be due to accumulation of water than of fat. Œdema, rising blood-pressure and protein in the urine are the signs of established pre-eclampsia which, if not properly treated, may lead on to eclampsia. The prevention of severe pre-eclampsia and eclampsia, the cause of which is still unknown, is more a matter of a high standard of antenatal care than of dietary measures.

STILLBIRTH RATES, PERINATAL MORTALITY RATES AND MATERNAL MORBIDITY RATES.—The policy of food rationing in Great Britain during the Second World War and the placing of pregnant women in a priority class which received extra rations of milk, cod-liver oil and fruit juice, greatly improved the diet of women belonging to the lower socio-economic class. This measure was undoubtedly a factor in causing a fall in the *stillbirth* rate from about 38 to 28 per 1000. The fall was greatest in South Wales where unemployment had been high before the war started. This decrease appears less significant when it is restated as follows : After the institution of priority rationing during the war, 97 per cent. of pregnant women in Great Britain had a live child, compared with 96 per cent. before the war. Millis (1952) has also produced data to support the view that the decrease which occurred in Singapore between 1947 and 1950 in the *maternal mortality* rate and the *neonatal* and *infant* mortality rates may be the result of better nutrition of the mother and child. It is, however, necessary to remember that subsequent to the reoccupation of Malaya by the British Army, there was not only an improvement in the diet of the people, but that Medical and Health Services were re-established. It is always difficult to determine the extent to which diet, as distinct from other environmental factors, including medical care, influences beneficially or adversely the outcome of pregnancy.

When comparing international statistics of the effect of pregnancy on the mother and infant, the problem is complicated by racial factors.

Thus, in Hong Kong, the stillbirth rate is surprisingly low when one takes into account that a high proportion of the Chinese families are of refugee origin and live in grossly depressed conditions. Although obvious deficiency diseases, such as beriberi, have practically disappeared during recent years, it is difficult to believe that the diet of such women in Hong Kong is satisfactory. A recent joint investigation of the situation by the staffs of the University Departments of Obstetrics in Hong Kong and Aberdeen (Baird, personal communication) showed that the incidence of most causes of stillbirths, including pre-eclampsia, and of fœtal malformation was lower in Hong Kong than in Aberdeen.

Diet in Pregnancy

There are no ' special diets ' for pregnancy, nor are there any particular foods that must be taken or avoided. Nevertheless, most pregnant women require some general dietary advice as to how best to modify their usual diet so as to supply the extra needs for nutrients. The detailed nature of this advice will depend on the economic status of the family and the foods available.

The extra allowances for nutrients during pregnancy, as set out by the Nutrition Committee of the British Medical Association and the Food and Nutrition Board of the U.S.A. National Research Council, have been given (Tables 15, 1 and 15, 2, pp. 254, 255). Some of the physiological considerations behind these recommendations have been discussed in Part I.

To account for the fact that pregnant women living on poor diets have often been observed to show surprisingly little evidence of malnutrition, Beaton (1961) has suggested that ' adaptive changes take place in the pregnant woman to minimise the requirements for protein, iron and calcium.' This is a sensible idea and in his paper Beaton presents evidence that pregnant rats can utilise protein more economically than non-pregnant animals. There have as yet been no reports giving experimental evidence of adaptive changes of any sort in pregnant women ; human adaptation to low calcium intakes has been clearly demonstrated (p. 163), but whether or not this occurs in pregnancy is unknown.

Calcium.—The extra needs for calcium to make the bones of the fœtus are best met by increasing the milk intake. At least 1 pint (about 0·5 *l.*) of milk should be taken daily. This will supply about 600 mg. of calcium, nearly half of the recommended allowance. Because of the greatly increased demands for calcium and protein in the later months of pregnancy, many obstetricians recommend the consumption of 2 pints of milk daily. Page and Page (1953) claim that if this quantity of milk is drunk, the tendency to leg cramps in pregnancy which appears most frequently between the twenty-fourth and thirty-sixth weeks of gestation, is greatly increased. This they attribute to increased neuromuscular irritability, mainly due to a decrease in the ionized calcium of the blood and a rise in the inorganic phosphorus concentration. This paper is frequently referred to in standard works on obstetrics, but we are not aware of any independent controlled observations which support the above biochemical and clinical findings. Hence, we are not prepared to recommend that the drinking of 2 pints of milk daily during the last trimester of pregnancy is contraindicated.

If milk is not available or the patient cannot afford it, liberal amounts of vegetables rich in calcium (Table 11, 2, p. 158) should be taken, supplemented, if necessary, by calcium lactate given orally.

PROTEIN.—The increased need for protein will also be largely met by a pint of milk daily, which provides 18 to 20 g. In many countries poor women have to depend on cereals for their main source of protein. A good *mixture of plant proteins* must be taken and can be an effective substitute for milk (Chapters 5 and 28). Pulses are of value as a source of protein. Education on this point is of the greatest importance in the tropics.

IRON.—Anæmia is very common in pregnant women because of the increased demands for iron by the mother and fœtus (p. 464). Of 1071 patients seen in Edinburgh in the first 11 weeks of pregnancy (Kerr & Davidson, 1958*b*) 32 per cent. were mildly anæmic (hæmoglobin level less than 12·6 g./100 ml., or 88 per cent.). The reduction in hæmoglobin levels was due to anæmia and not to physiological dilution of the blood as this is minimal during the first trimester of pregnancy. A considerably higher incidence of iron deficiency anæmia in pregnancy has been reported from many parts of the world, including elsewhere in Great Britain (Giles & Shuttleworth, 1958). Even women with high initial levels often have a large fall in the second or third trimester. For these reasons we recommend: (1) a liberal diet with a good supply of meat, fruit and vegetables; (2) routine hæmoglobin estimation at the first visit to an antenatal clinic; (3) iron therapy for all patients with an initial hæmoglobin level of less than 12·6 g./100 ml. (85 per cent.); (4) routine therapy with iron for all patients from the twenty-fourth week to term. This should be taken in the form of one pill containing 3 gr. (180 mg.) of ferrous sulphate three times a day, which provides a total of 180 mg. of elemental iron daily. This will raise the hæmoglobin levels in most women, and in our opinion is a valuable prophylaxis against anæmia.

VITAMINS.—Milk, fruit and vegetables in adequate amounts can supply all the necessary vitamins. If a good mixed diet is eaten there is no need to prescribe any vitamin supplements. When there is any doubt about the quality of the diet, a concentrated fruit juice and vitamin A and D tablets or a fish-liver oil should be given. In Great Britain these Welfare Foods (Chapter 51) can now be obtained at cost through the Maternity and Child Health Services. The advisability of giving a small daily supplement of synthetic folic acid routinely to all pregnant women during the last trimester of pregnancy is at present a controversial matter. By this means the potentially severe and dangerous megaloblastic anæmia of pregnancy (p. 652) can certainly be prevented. If, however, pregnant women are going to have a proper hæmatological check-up during pregnancy, it seems to us unnecessary to give routine prophylactic treatment with folic acid. In underdeveloped countries, where the diet and medical service are inadequate, the matter is different.

CALORIES.—The problem of the caloric requirements of pregnant women is difficult. Extra calories are required for the growth of the fœtus and also to meet the increased physiological needs of the mother (p. 33). The provision of these calories has been discussed in Chapter 2, where it was pointed out that in some social circumstances they are likely to become available through a restriction in physical activities; then there is no necessity for an increase in the quantity of the diet. This is important, for there is no doubt that an excessive intake of calories (as judged by the weighing machine) is harmful. A proper balance between energy intake and energy output is necessary. Many women, especially those responsible for the care of young children, lead a very active life when pregnant. Others, particularly, primigravidæ who live in towns, may reduce their normal physical recreations. For such it is better to continue their recreations rather than to reduce the intake of food. Many hobbies and sports can be continued in a modified form until the last trimester of pregnancy, and this is to be recommended provided very strenuous activity is avoided. In the last few weeks walking is the most satisfactory form of exercise. Experience in many clinics has shown that it is often difficult to get pregnant women who are not gaining weight satisfactorily to put on weight, and vice versa—to achieve a satisfactory loss of weight in those who have gained too much weight. This problem has been discussed in Chapter 27.

Any marked departure from the normal rate of gain demands attention. A pregnant woman should be weighed monthly up to the twentieth week of pregnancy; thereafter she should be weighed and examined once every one or two weeks. If she has gained no weight at all, or if she has gained too much weight she should be given a full medical examination; if no pathological explanation can be found, she must be advised either to increase or reduce her diet. All obstetricians are agreed on the undesirability of an excessive gain in weight during pregnancy. This weight may not be lost after delivery and with successive pregnancies frank obesity may develop, with its harmful effects (p. 386).

General advice.—During pregnancy bizarre appetites may develop. Some women have a greatly increased appetite and this may lead to gross obesity with all its ill-effects. In others there may be a longing for some unusual article of food. Such bizarre appetites and temper tantrums are much less common to-day than 40 years ago. The explanation for these whims is uncertain. Pregnant women should be told frankly that such behaviour and cravings are not a normal accompaniment of pregnancy but are not serious. An effort should be made to correct them by simple explanation and encouragement.

With regard to the need for fluid, milk has already been recommended. A glass of water immediately on rising in the morning and at each main meal is desirable ; tea, coffee, beer and wines may also be taken in moderation.

There is no need to restrict the intake of salt provided it is taken in moderation unless œdema is present. The evidence supporting the view that salt restriction reduces the incidence of the toxæmias of pregnancy and hydramnios is far from convincing.

PATHOLOGY OF PREGNANCY

Vomiting in Pregnancy

Morning sickness.—In the early weeks of pregnancy most women suffer a little from nausea, especially in the early morning, and there may be vomiting. The cause of this is not known. ' Morning sickness ' is certainly not psychological in origin, although psychological factors often aggravate the symptoms. It may be presumed that the symptoms arise from some metabolic or endocrine change brought about by the presence of the fœtus, to which adjustment is usually quickly made.

There are innumerable ' old wives ' remedies for morning sickness, but unfortunately no scientific treatment. The patient should be reassured that the condition will shortly disappear. Symptomatic treatment with sedatives may be required. Anti-emetic drugs which are of proved value for the treatment of motion sickness, such as promethazine chlorotheophyllate (Avomine), 25 mg. twice daily, and meclozine dihydrochloride (Ancolan), 50 mg. twice daily, have proved very helpful to some patients (Diggory & Tomkinson, 1962). If there are associated psychological disturbances, they will require treatment. If the vomiting persists or becomes severe, some additional factor is responsible and a full medical examination is necessary.

Hyperemesis gravidarum.—In some pregnant women, both primigravidæ and multigravidæ, morning sickness and nausea become progressively worse. Vomiting may persist throughout the day so that neither fluid nor food is retained. When this occurs the disorder is called hyperemesis gravidarum. The cause is not known but a psychological element is certainly a contributory factor. The resulting metabolic changes may be mild or moderate in degree or so severe as to be lethal. The patient should be immediately removed to hospital, and in many cases this measure alone rapidly leads to a cessation of vomiting. If this does not occur it will be necessary to correct the dehydration, ketosis, hæmoconcentration and the electrolyte imbalance due to loss of chlorides which are the consequence of vomiting and nausea ; the patient must receive ample amounts of fluid, carbohydrates and sodium chloride. While these can be given by mouth to mild cases, they must be introduced by gavage or intravenously in severe cases (Chapter 48). With improvement of the patient's condition, which usually occurs within a day or two of admission to hospital, the dietetic ladder can be gradually climbed as described in the treatment of a severe attack of acute gastritis (p. 503). When treatment is actively carried out on the lines discussed, the prognosis is very good.

Pre-eclampsia

The term ' toxæmia of pregnancy ' is widely used to describe a group of disorders characterised by the appearance of raised blood pressure, œdema and albuminuria which may develop for the first time during pregnancy or may be present prior to, but be adversely affected by pregnancy. Examples of the former group are pre-eclampsia and eclampsia, and of the latter group pre-existing essential hypertension and chronic pyelonephritis. Hyperemesis gravidarum is no longer classified as one of the toxæmias of pregnancy. In the following pages we are concerned especially with the dietetic treatment of pre-eclampsia and eclampsia. As has already been mentioned, the fundamental cause of these diseases is not known so that prophylaxis is not possible, while treatment of the established disorder is essentially symptomatic. Before discussing the management of a patient with pre-eclampsia or eclampsia it is desirable to define these disorders arbitrarily by reference to the severity of their predominant physical signs, namely the height of the blood pressure, the degree of œdema and the extent of the urinary changes, *i.e.* albuminuria, hæmaturia, oliguria or anuria.

Mild pre-eclampsia.—The patient feels well but examination reveals that the blood pressure is slightly elevated, *i.e.* systolic pressure 140 to 160 mm. Hg., and diastolic pressure 90 to 110 mm. Hg. There may be slight œdema of the ankles and a trace of albumin in the urine. The urinary output is well maintained and the specific gravity is normal.

Severe pre-eclampsia.—The systolic blood pressure is over 160 mm. Hg. and the diastolic pressure over 110 mm. Hg. In addition the œdema is increased in degree and may extend to the hands, face and abdominal wall. Albuminuria may reach massive proportions, *e.g.* as high as 10 to 15 g./*l.* In very severe cases other serious features are headache, disturbances of vision, vomiting and oliguria.

Treatment.—Early diagnosis is the sheet anchor of good antenatal care, since treatment may prevent the disease from progressing to the severe stage of pre-eclampsia or eclampsia. For mild pre-eclampsia modified rest, *i.e.* 2 hours rest in bed in the afternoon, and adequate sleep, achieved if necessary by the use of a sedative or hypnotic drug, are of prime importance. It is unnecessary to restrict fluids or protein foods, since renal function is satisfactory. Salt should not be added to food at table and should be used sparingly in its preparation. A thiazide diuretic may be given if œdema is present. In severe pre-eclampsia the prognosis is uncertain and may be grave, and the patient should be treated in hospital by a team of experts in this field. If severe pre-eclampsia develops in a patient approaching term, pregnancy should be immediately terminated by the induction of labour. If it occurs at an earlier stage of pregnancy, management should be on the following lines.

The blood pressure should be taken 4-hourly and the volume, specific gravity, content of albumin, the presence of cells and casts in the urine, and the level of blood urea should be charted daily. In addition to complete bed rest, and the administration of adequate amounts of sedative and hypnotic drugs, the protein intake must be reduced to a figure which will depend on an estimation of the degree of renal function. This problem has been discussed at length in Chapter 41. Diet No. 18 is a restricted protein diet containing 60 g. of protein daily, while diet No. 16 is a low protein diet containing approximately 45 g. of protein daily. If vomiting is a marked feature, the patient may be able to take only small amounts of milk and diluted fruit juice at 2-hourly intervals until improvement occurs. A thiazide diuretic should be given for the treatment of the œdema, and if this produces a good diuresis the patient may be allowed 1 to 2 *l.* of fluid per day. Salt should be restricted according to the degree of œdema and hypertension. The problems related to sodium restriction have been fully discussed on pages 570 to 572. The restricted salt regime will reduce the intake of dietary sodium to about one-third of normal, while the low sodium diet (No. 14) will reduce the daily sodium intake to approximately 0·5 g. This diet is also low in protein.

Symptomatic treatment for headache and vomiting will be required and hypotensive drugs are clearly indicated if the blood-pressure is excessively high. The indications for and use of hypotensive drugs are discussed on page 564. Treatment on the above lines, if undertaken early and carried out effectively, usually produces a great improvement within a few days. Should treatment not be successful or signs of impending eclampsia appear, pregnancy should be terminated immediately.

Eclampsia

The great majority of cases of eclampsia have already passed through the stages of mild or severe pre-eclampsia. The vital importance of early diagnosis and effective treatment of pre-eclampsia in the prevention of eclampsia cannot be emphasised too strongly. The onset of eclampsia is recognised by the development of epileptiform convulsions which pass through tonic and clonic phases and are usually followed by coma. The other features of severe pre-eclampsia also occur. The urinary changes are even more marked and red cells and casts in addition to a massive albuminuria are present. When severe oliguria (less than 200 ml./day) or anuria occurs, the output of nitrogen in the urine diminishes and correspondingly the level of urea in the blood rises. The medical treatment of eclampsia in so far as it concerns œdema, hypertension, headache and vomiting is the same as that described for severe pre-eclampsia. In addition, the fits must be treated by bed rest, quietness, good nursing and the use of sedative drugs such as bromethol 0·09 ml./kg. body weight, per rectum. When marked oliguria or anuria develops treatment consists in giving glucose 100 to 300 g. daily and fluid in limited quantities (500 to 1000 ml. daily) intravenously or by intragastric drip. Treatment is the same as that for patients suffering from acute renal failure and acute tubular necrosis (pp. 587 to 589). Obstetricians are agreed that because of the real risk to life of the mother, pregnancy should be terminated if labour has not commenced shortly after the onset of the convulsions, which it usually does.

LACTATION

The same general principles apply as during pregnancy. The recommended allowances for nutrients are given in Chapter 15. The mother who is breast-feeding her baby requires a good all-round diet, especially if she is doing active work in the house, shop or factory ; otherwise she will lose weight and become easily tired. If she is to provide the infant with 2 pints of milk daily this will require an additional 600 Calories. The considerable increase in body fat gained by many women during pregnancy can be used to meet this demand without increasing the diet and with a corresponding beneficial reduction in weight. If the obese mother decides to wean the infant shortly after its birth, a reducing diet must be prescribed (p. 389). The weighing machine will provide evidence as to whether the mother and her baby are getting too little or too much nourishment. The extra calcium and protein required by the lactating mother are most conveniently provided by milk. If possible, at least 1 pint a day should be drunk and preferably more. Since a lactating woman may be producing 2 pints of milk daily it is obvious that she should take adequate amounts of fluid. There is, however, evidence to show that by forcing her to take large amounts of fluid, neither the quantity of the milk is increased nor its quality improved (Illingworth & Kilpatrick, 1953). Tea and coffee, as well as beers and wines, may be drunk in moderation and will not alter the quality of the milk. Many drugs in common use are excreted in the milk, but in such small amounts as to cause no ill-effects to the infant. A few drugs are potentially dangerous and if it is essential that they should be given to the mother, breast-feeding must be discontinued. Examples are antithyroid drugs such as thiouracil which may cause hypothyroidism in the infant, barbiturates and possibly phenytoin when given in large dosage to epileptic mothers.

It is well known that the supply of milk will be maintained even if the mother's diet is inadequate. Her own stores of nutrients will be drawn upon and evidence of malnutrition will appear in the mother before it does in her child. An excellent study of lactation in poor Indian communities made by Gopalan (1958, 1962) shows the remarkable ability of poor women to breast-feed their infants for long periods. How to obtain improvement in the diets of poor mothers in underdeveloped countries, especially in regard to the quantity and quality of the protein intake, constitutes an important public health problem in many parts of the world.

Even for a healthy woman with a good diet, the provision of sufficient milk to meet *all* the needs of a vigorous infant weighing 12 lb. (5·5 kg.) or more is a considerable physiological strain. Supplementary feeding, *i.e.* the substitution of a bottle feed for one or more breast feeds, may be indicated. The introduction of egg yolk, cereals, meat and vegetable broths and purées and other easily digested sources of iron should begin at four months approximately, and thereafter weaning should proceed gradually. This is best achieved by the omission of one breast feed each week over a period of five weeks. It should usually be completed during the eighth month.

In countries where the milk supply is inadequate and many families get little or no milk, it is a great advantage for the infant to continue to get a little breast milk. In such circumstances, if limited to *one or two* small feeds daily, this practice can be continued without harm to the mother until the child is 2 years old.

CHILDHOOD

During the first year of life, milk is the dominant food. Carefully controlled investigations have failed to show any significant difference in the stature and physical or psychological health of infants fed with human milk and those fed with cow's milk suitably modified (p. 311). The introduction of dried cow's milk has made artificial feeding not only simpler than formerly, but safer because of the reduced chance of bacteriological contamination. Suitably diluted dried milk powder has the additional advantage over fresh cow's milk that it is possible to give larger amounts of nutrients in smaller, less diluted feeds.

Nevertheless, breast feeding is a physiological process which is the natural consequence of pregnancy. Frequently it is a satisfying experience which gives much pleasure to both mother and infant; hence it should be encouraged provided that lactation is adequate for the infant's needs. However, some women, especially in wealthy and sophisticated communities, positively dislike feeding their infants at the breast, while others find that it interferes excessively with their social, professional or business activities. Such women tend to have inadequate lactation and it is better to allow artificial feeding to be started, rather than to insist on the mother continuing with a procedure which she finds frustrating and unsatisfying. In underdeveloped countries where poverty makes the purchase of adequate quantities of milk difficult or impossible, and where the facilities for obtaining clean milk are poor and the methods of sterilising the baby's bottle are unsatisfactory, it is essential to do everything possible to get the mother to breast-feed her infant. Moreover, as a measure for the prevention of kwashiorkor, breast feeding can be continued without harm to the mother until the child is 2 years old, provided it is limited to one or two *small* feeds daily.

No attempt is made here to discuss in detail diets during infancy, as these are dealt with in many excellent textbooks of pædiatrics.

Milk.—A child at the age of 1 year needs about 1000 Cal. daily. If he is getting 1 pint (about 0·5 *l.*) of cow's milk daily (a satisfactory allowance) then about 35 per cent. of the calories are derived from milk. The remainder of the calories are provided by a mixed diet—in practice usually of the same quality as that of the rest of the family. As the child grows and the need for calories increases, the proportion provided by milk falls and the diet gradually approaches the adult pattern.

The value of milk as a food for children has been established by practical experience and put on a scientific basis by Corry Mann (p. 733) and many others in controlled field trials. It is desirable that every child up to the age of 5 should have at least 1 pint (0·5 *l.*) daily, and after 5 until growth ceases at least half a pint. Milk is chiefly valuable as a source of good-quality protein and of calcium needed for growth. In practice, growth and development are usually slow in children who receive poor diets containing little or no milk. This need not be so, for McCance and Widdowson (Chapter 17) showed that if a good mixture of vegetable proteins is provided excellent growth rates are obtained, despite the virtual absence of milk from the diet.

Larger amounts of milk are sometimes recommended. These will accelerate growth still further and, less certainly, increase the adult size, but there is no evidence that either is desirable or contributes to health and well-being.

Vitamins.—Requirements for vitamins are relatively increased in childhood and it is well known that children are more liable than adults to many deficiency diseases. Often the family diet is not satisfactory; then it is desirable to provide daily for the child extra vitamin C in the form of fruit juice and extra vitamins A and D in the form of a fish-liver oil. The beneficial effect of these Welfare Foods (p. 735) has been repeatedly demonstrated. A great increase in their supply is needed in many countries. As already mentioned, in Great Britain these Welfare Foods can be obtained at cost price through the Maternity and Child Health Services. After the age of 2 years, provided the child is healthy and eats a good mixed diet including fruit and vegetables, there is no necessity for these extra vitamins.

The normal child does not need synthetic vitamin tablets unless there is a specific indication. A serious illness, hypercalcæmia, due either to vitamin D intoxication or to sensitivity or idiosyncrasy to vitamin D (p. 166) is attributable in some cases to excess vitamin D, either added to infant foods or given in tablets.

Calories.—The recommended allowances for nutrients given in Chapter 15 are a useful guide for those responsible for feeding large numbers of children in schools and orphanages. They form a basis on which practical ration scales can be drawn up. However they are no guide to the needs of an individual child. Children vary greatly in their intake of calories and a healthy child may need only half, or more than double, the allowance. If given the opportunity, many children and most adolescents of both sexes have an enormous capacity for games and physical recreations. Their food requirements are then much greater than is indicated in the tables in Chapter 15. Conversely, if they become accustomed to watching television or engage in other sedentary recreations they require less.

Appetite is normally a sound guide to requirements. Children's feeding behaviour is far less a matter of habit than adults. A child may eat voraciously for a day or two and then lose all interest in his food for a while. This is natural and there is no necessity to restrict his meals in one phase or to attempt to force food during another. Many children occasionally develop specific appetites for one food. This may make the diet temporarily quite unbalanced. This again will do no harm for it will soon be rectified naturally, and so need not be checked unless it offends against good manners.

The best guide that the food intake is satisfactory is provided by the weighing machine. It is sound practice to weigh and measure the height of a child every three months. Provided the increase in weight and height is satisfactory (Tables 50, 5 and 6 are useful rough guides) there is no need to worry about a child's diet

The management of children's diets

A child's diet is best taken equally divided between three main meals. Breakfast is usually taken with the family. It is a meal which is frequently skimped by adults, who may indeed do well with very little food in the morning. It is however essential for children to go to school with a good breakfast inside them. The midday meal may be taken either at home with the family or at school. Young children under 5 must go to bed early and it is best for them to have their evening meal separately before the rest of the family. If the main family evening meal is taken after 7 o'clock, children under 10 will also need a meal earlier.

In many countries it is customary to give school children a glass of milk at the mid-morning break and this is sound practice. If the evening meal is late, children will want something in the middle of the afternoon. This is permissible. Otherwise children are best without snacks between meals. Eating ' bits and pieces ' at irregular hours is liable to spoil the appetite for the main meals and is to be avoided.

Sweets and candies.—An excessive consumption of these will also spoil the appetite for the main meal and so should be forbidden. There is also considerable evidence that they predispose to dental caries (Chapter 54). Nevertheless taken in moderation, especially after meals, they will do no harm and are a legitimate pleasure of childhood. The danger of excessive consumption is always present and there is need for discipline and self-control.

CHAPTER 58

NUTRITION AND THE CARE OF THE AGED

DEFINITION OF 'ELDERLY' AND 'OLD'

IT is often said that a man is as old as his arteries and there is much justification for this saying. People with advanced degenerative arterial disease at the age of 60 may have the stigmata of old age, while others with healthy arteries and a normal blood-pressure may continue to lead an active physical and mental life till 80 years and more. In other words age in years does not necessarily coincide with biological age.

It is impossible to state accurately when ageing begins. Many of the tissues of an infant 6 months old differ markedly in chemical structure and histological appearances from those of a newborn infant. As Ham and Leeson (1961) record, the tissues of a fœtus are jelly-like because of their high content of amorphous intercellular substance, and those of a newborn infant have much less fibrous intercellular substance than those of an adult. As the years pass the fibrous elements are built up and the amorphous intercellular substance gradually becomes less. This characteristic ageing process certainly starts *in utero* and goes on throughout life. However it can hardly be said to be pathological. More obvious evidence of ageing is the steady increase in the mean values for body weight, blood-pressure and plasma cholesterol, which occurs in all prosperous human communities. As described in previous chapters, these increases are almost accepted as physiological features of middle age. However, the rise in each of these three factors has been clearly demonstrated by the age of 25. If they are accepted as evidence of the 'ageing process,' it certainly begins to operate soon after the twenty-first birthday when traditionally a man comes of age.

Since there is no specific test for biological age, which is judged on the basis of overall impressions and external appearances, and because individuals differ so greatly in their physical and mental attributes with advancing years, it is extremely difficult to define the terms '*elderly*' and '*old*.' However, since the age of retiral is usually around 65, it seems not unreasonable to define as *elderly*, persons in the age group 65 to 75, while people beyond the age of 75 can be classed as *old*. The term 'aged' is used to cover both groups.

THE SIZE AND IMPORTANCE OF THE PROBLEM OF LONGEVITY

The population of England and Wales in 1959 was 45,000,000, which included approximately 5,400,000 (11·8 per cent.) persons aged 65 or more. Nearly 2,000,000 were 75 years old or more. The rapidity of change in age incidence is indicated by the following statistics. At the beginning of this century 1 in 21 of the people in England and Wales were 65 years of age or more. To-day the proportion is 1 in 9 and it is estimated that within another two decades the figure will be 1 in 7. The same trends have been demonstrated in the U.S.A., the Federal German Republic and other countries with a high standard of living and well-developed medical and social services. At the present time, and even more so in the years to come, this large and ever-increasing number of *elderly* and *old* people has created immensely important social, medical and economic problems. It is therefore of paramount importance that the most careful thought should be given to the investigation of any measures which might delay or ameliorate the mental and physical changes which accompany senescence so that elderly and old people can become less of a burden on the State, on their families and on themselves. Rolleston (1932) in his book defined old age as a progressive diminution in functional activity and described the clinical features fully. Franklin (1960), in an address to the Nutrition Society, summarised Rolleston's account as follows :—

> The response to stimuli of all kinds is diminished, the skin is dry and the hair usually more scanty and often getting whiter ; there is less intestinal secretion of mucus, and perhaps thereby a tendency to constipation ; thyroid secretion is less. Sensibility to pain decreases, but there is increased sensitivity to cold. Taste and smell are impaired, presbyopia and a contracted state of the pupils and sluggishness of the irides arise, while weakness of the orbicularis palpebrarum muscle may tend to ectropion and epiphora ; there may be reduction in the acuteness of hearing, and the appetite may be capricious. Muscular movement is slow and somewhat uncertain, the tendon-jerks sluggish and tending to go, and sleep is less continuous. Psychical activity diminishes, and the higher faculties go first ; initiative, originality and sense of humour fail, new ideas and fresh lines of thought are assimilated with difficulty. There is mental fatigue and less agile memory for names, anecdotage, a tendency to mislay things, and unconscious carelessness about personal appearance and habits. Affection wanes, and new friendships are formed with difficulty. There is selfish dependence and demands on friends. Senile vanity is not uncommon ; all old people love to be in the centre of the stage, one of the most pathetic things in life being that they are seldom allowed to be there. There is a passionate, absorbing, almost bloodthirsty clinging to life ; the pulse rate is usually raised, high blood-pressure without renal disease is common. The urine is somewhat less in quantity and there is a fall in its solids. Sexual activity is usually less after 50, and wounds and fractures heal more slowly, though age *per se* is no bar to operations. The physiological response to drugs is slower and more prolonged.

This picture, though unfortunately true for some old people, is unduly pessimistic. Inevitably with increasing years the pace of life must be slowed down. Adjustments, both physiological and psychological, are more difficult and take longer. However, there have been many people who have remained healthy and active both in body and mind to the age of 100 years or even more. Even after the age of 90 life can still be enjoyed and many of the very old are charming in their manners and capable of retaining and also making friendships.

The Prevention of Senescence

It is probable that once biological old age has been reached the condition is irreversible, but it seems reasonable to assume that various measures may be available which might at least slow down the ageing process. There are two main factors which influence the life span, namely the genetic factor and the environmental factor, and by far the more important is the former. If we could make a judicious choice of our parents, our chance of living to a ripe and healthy old age would be greatly increased. There is also no doubt that physical and mental activity after retiral plays an important part in postponing the onset of morbid old age. Likewise, it is always important to prevent and treat infections and infestations effectively with modern drugs and antibiotics, and to prevent and treat nutritional disorders due to deficiency of protein, vitamins or minerals, by appropriate dietetic measures. At first thought it might appear obvious that the more adequate and better-balanced diet which has been eaten by the majority of the people in Great Britain, Western Europe and the U.S.A. has played an important role in increasing the life span so spectacularly in the last 30 years, but it must be remembered that many other factors, including better sanitation, better housing and modern chemotherapy, have all been operating simultaneously. Coincidental with this improvement in nutrition there has occurred a remarkable increase in the height and weight of children and adolescents of the working classes. Whether these children will survive to an older age accompanied by increased mental and physical well-being is a problem which cannot be answered for many years to come.

There has been much study of the effects of diet on the length of life of experimental animals. In this work McCay (1949, 1955) at Cornell University has been a pioneer. Many carefully controlled investigations into the effects of giving to insects, fish and mammals a diet which leads to a rapid increase of growth and weight, have actually shown a reduction in life span. In addition such a diet has been shown to produce in rats and mice an increased liability to degenerative diseases and various tumours, including carcinoma. The reverse was found to occur when the calorie intake was below the optimum for rapid growth. Rats, whose growth has been retarded by restricting their food intake, have lived much longer than controls fed unlimited amounts of food. Although much more information must be available before it would be justifiable to accept these results from animal experiments as being necessarily applicable to man, they certainly draw attention to the question of whether maximum growth rates are desirable and they clearly indicate the possible harmful effects of over-nutrition which is so common in many prosperous countries at the present time.

DIETETIC REQUIREMENTS OF ELDERLY AND OLD PEOPLE

Measures for the prevention and treatment of diseases of *elderly* and *old* people by diet cannot be satisfactorily defined until much more information is available in regard to the physiology, biochemistry and pathology of senescence. A detailed investigation is going on in Glasgow into both the dietary habits and physical activities of elderly people. Preliminary reports (Durnin *et al.*, 1961 ; Durnin, 1961*b*) indicate that many of them remain physically active and consequently require a large and varied diet. Others have slowed down very markedly even in their early sixties. There is no evidence that the qualitative nature of the diet is unaltered. Further clinical and metabolic studies are needed, but are difficult to design, mainly because degenerative changes (*e.g.* senile osteoporosis, Chapter 30) proceed very slowly. In such studies the units of time must be months and years rather than days and weeks.

TABLE 58, 1. *Intakes of protein, judged to be necessary for equilibrium in women at various ages*

Age years	Number of subjects	Nitrogen intake g./day
30–39 . .	25	10·6
40–49 . .	34	11·0
50–59 . .	40	11·2
60–69 . .	25	10·8
70 + . . .	11	9·4

Calorie requirements.—Since physical and metabolic activity is reduced in *old* people, a reduction of some 20 to 30 per cent. in their calorie intake as compared with the age group 20 to 30 is desirable (Chapter 2). A similar reduction is also desirable for many *elderly* persons but not for those who continue to work actively in the field or factory. It is essential that obesity should be avoided because of the many undesirable effects which may result (p. 386).

Protein requirements.—It has been stated that the amount of protein required by the elderly is less than that necessary for young or middle-aged people, because there is no need for protein for growth or development and because ‘ wear and tear ’ of tissues may be diminished and thus needs for maintenance are less. On the other hand, it has been suggested that for the prevention of progressive tissue wasting, which is such a feature of old age, the intake of protein should be increased. Ohlson and her colleagues (1952) carried out balance studies on 136 American women aged 30 to 85 years. Table 58, 1, summarises their conclusions. From this evidence there is no reason to think that the recommended allowances of protein for adults needs to be either increased or decreased with advancing age. Hence we suggest that the needs of the aged will be met if the protein intake is approximately 1 g./kg./day, *i.e.* about 65 to 70 g. daily. If possible a quarter to one-third of this quantity should be obtained by taking a pint of milk daily as liquid milk or in puddings, as by this means the calcium requirements will also be largely satisfied.

Fat intake.—Since old people are prone to develop degenerative diseases of the cardiovascular system some may consider, for the reasons given in Chapter 40, that their total intake of fat should be reduced and in particular their intake of saturated fats, *e.g.* animal fats and the fats of dairy products. They would advocate that not more than 20 to 25 per cent. of the total calories should be provided by fat, in contrast to the figure of 40 per cent. or more which is commonly eaten by persons living in prosperous countries. We would not advocate any rigid restriction of fat in the diet of a healthy *elderly* or *old* person. Excesses are to be avoided. A daily intake of 75 g. of fat provides 30 per cent. of the energy in a diet of 2000 Cal. This seems a reasonable compromise, which can be recommended to those responsible for drawing up diet schedules for old people's homes.

Carbohydrate intake.—Approximately 250 to 300 g./day of carbohydrate will be required in addition to the amounts of protein and fat recommended above if the total calorie intake is to be about 2000 to 2250 g. This figure will obviously need to be adjusted according to the medical assessment of the case. Some elderly persons, because of poverty, physical incapacity, apathy or lack of appetite, are undernourished and underweight, and they will require an increase in the amount of carbohydrate and possibly an improvement in the intake of protein, vitamins or minerals. Many elderly people are obese and for them a reduction in the intake of carbohydrate is essential.

Vitamins.—It has been claimed that aged persons need an intake of vitamins higher than the usually accepted recommended allowances because of their reduced capacity for alimentary absorption, changes in bacterial flora of their intestine and increased endogenous requirements; but satisfactory evidence of these claims is wanting. Clinical experience, however, shows that old people who are poor, apathetic or mentally or physically handicapped tend to take a diet deficient in various nutrients and in particular in vitamin C and the B complex. Bachelor's scurvy is not rare amongst old men living alone. Hence, physicians in charge of the elderly should take a careful dietary history and search for those stigmata described in Chapter 37 which indicate the possibility of nutritional deficiencies. For healthy *elderly* and *old* people there is good reason to believe that the recommended allowances for the various vitamins, as discussed in Chapters 13 and 14, are adequate. It is particularly important that a helping of fresh fruit or green vegetables should be taken daily.

Minerals.—Demineralisation of the skeleton is a frequent cause of fractures in the elderly and so responsible for much ill-health and disability. Such fractures may make heavy demands on hospital accommodation and nursing services. Senile osteoporosis has been discussed in Chapter 30. It is uncertain to what extent the wasting of the skeleton is caused by a failure to maintain the protein matrix or by a failure to provide calcium salts in adequate amounts. Hence, it seems reasonable to recommend that the raw material necessary to maintain the skeleton, principally protein and calcium, should be supplied in the same amounts to the *elderly* folk as in the recommended allowances for adults. This means an intake of 1 g. calcium a day. This can be easily obtained if the diet contains dairy products such as cheese and milk. At the present time in Great Britain the chalk added to the bread (p. 268) makes a significant contribution to the daily calcium intake of most of us.

Milk can be recommended to the elderly as a good source of both protein and calcium in forms which are easily digestible and absorbed. Most elderly people would benefit from a pint of milk a day. This may present financial difficulties which must be met. We know of no experimental study designed to show the effect of the addition of milk to the diet on the health of the elderly. The beneficial effects of milk in improving the health of undernourished children have often been shown to occur in a matter of weeks. In the elderly it might take months or years for them to become apparent. Such trials might well prove worth while.

The physician should remember the possibility of anæmia developing in the elderly, especially if the diet is poor in protein and green vegetables. If it is found to be present, it must receive the appropriate medicinal treatment because of the adverse effects which anæmia has on the physical and mental health of the aged.

MEDICAL CARE OF THE AGED

As already indicated there are great variations in the nutritional requirements of *elderly* and *old* people, both in health and disease; in consequence there can be no standard dietary schedules applicable to the aged. This applies equally to all forms of medical treatment. It is not uncommon for those whose duty it is to care for the aged sick, to think that the disorders and disabilities of old age are incurable and that occupational therapy and physical rehabilitation are the only therapeutic measures worth employing. Such an outlook must be energetically opposed. The primary requirement for the treatment of the aged is accurate diagnosis, followed by medical treatment based on modern scientific principles. Much can be done by the doctor to alleviate the infirmities of the aged by seeing that they get a good mixed diet in quantities sufficient to meet their legitimate appetite, by obtaining for them suitable dentures, spectacles and hearing aids, and by ensuring that their corns are treated regularly by a chiropodist. Antibiotics and other drugs are just as valuable in the aged as in the young. With modern anæsthesia, the surgical treatment of piles, a rupture, a prolapsed uterus or enlarged prostate is usually possible and the results well worth while. Thereafter occupational and physical treatment, if necessary, may be employed with great benefit.

Every physician looking after the aged should realise that frequently a considerable part of the disabilities and frailties of age are the result of emotional causes leading to a failure of morale and a lack of interest in living. This attitude of mind develops as a result of isolation, immobility, loneliness and poverty ; the doctor must make every attempt to deal with these problems by his own individual efforts and with the help of voluntary organisations and local and national health authorities. The care of the aged is as much a social problem as a medical problem. The doctor should have first-hand knowledge of the personnel and services provided by the health authorities in his district, *e.g.* home nurses, home helps, meals-on-wheels, special laundry facilities, residential accommodation in welfare homes and geriatric hospitals and financial aids from the National Assistance Board and other agencies.

Lastly, some of the problems and disabilities of old age would be lessened if persons about to retire gave adequate thought to this matter in good time, as by this means functional activity, mental and physical, could be better maintained for many years after retiral. This important subject is dealt with in a book called *Facing Retirement* (Country Doctor, 1960). In it will be found a great deal of information and advice on the social, medical and financial aspects of old age which will be a valuable guide to the middle-aged and elderly facing retirement.

In conclusion we would enter a plea for much more research into all aspects of the process of ageing, including nutrition. Until fuller and more accurate information is forthcoming, prevention and treatment must continue to be largely empirical because of fundamental gaps in our knowledge.

CHAPTER 59

ATHLETICS

ONLY a minority of athletic records are 10 years old. In all classes of athletics, and indeed in sports generally, there has been a sharp rise in the standards of performance. These new standards have been made possible by newer methods of training. Most important, the top-class athlete trains far harder than his predecessors. The extra physical activity in training involves extra energy.

In the past there was no sphere of dietetics in which faddism and ignorance had been more conspicuous than in the field of athletics. Sir Adolphe Abrahams (1956) has given an amusing account of some of the fantastic dietary customs that were common amongst athletes 50 years ago. Mayer and Bullen (1960) have provided a good review which separates the few established facts from the large volume of fiction which is still widespread about diet and athletics. It is now known that the dietetic requirements for the athlete in training are based on the same fundamental principles which govern the nutrition of human beings in general, as already outlined. These principles have been generally applied to athletes in training and this no doubt has contributed to some extent to the general improvement in athletic performances in recent years.

It can be stated categorically (1) that none of the ordinary foods eaten by man are either of special value or contraindicated in athletic training ; (2) that preparations of vitamins and minerals, given in addition to a good mixed diet, will not improve athletic performance ; (3) that alcoholic drinks taken in small quantities by people accustomed to them will have no effect on training.

Athletic training nearly always involves a large expenditure of physical energy and the energy required in the training schedule must be provided by the calories in the diet. Many athletes in training consume diets providing 4000 to 5000 Calories daily, though lower intakes are probably more usual. It is essential that adequate amounts of protein be provided and this is ensured if between 11 and 14 per cent. of the calories are provided by protein. Surveys have shown that many athletes take by choice larger quantities of protein than this, but there is no evidence that this extra protein is beneficial : nor does it do harm. Many first-class athletes have been vegetarians, and provided the protein intake is adequate, vegetarian diets are suitable for hard training. High caloric diets must contain large quantities of fat, unless they are to become very bulky. Physical activity prevents the disturbances in blood lipids which commonly arise in sedentary people on high fat diets (p. 107), and large quantities of fat in the diet will do no harm to men and women undergoing physical training. Provided the requirements for protein, carbohydrate, fat, minerals and vitamins are properly satisfied, the diet for the athlete in training differs only from the ordinary well-balanced diet in that it must provide extra sources of energy. The quantity of food required can usually be assessed by the individual's natural appetite, and no food schedules are required. At the beginning of a period of training, if the subject has previously been taking little physical exercise, there may be some loss of weight due to the using up of excess fat. Subsequently there will probably be a gain in weight, attributable to hypertrophy of muscles.

Many types of sport and athletics involve large losses of fluid in the sweat. Losses up to 1 *l.* in an hour are not uncommon. It is important that these losses are promptly made good by the necessary fluid intake. Even a very minor degree of dehydration may impair the efficiency of muscles. The restrictions on fluid intake often imposed by trainers of a previous generation must have done nothing but harm.

The problem of the food requirements immediately before an athletic event of short duration or during long-distance swimming and bicycle races is important. If an event does not last for more than an hour, there is no necessity to interfere with usual dietary habits. A normal meal should be taken about 2 hours before the event. During an event which lasts several hours some easily assimilated food must be taken. A racing bicyclist may be expending 600 Calories in an hour throughout the day. Part of this can be provided by stores of carbohydrate and fat already present in the body before the event, but some food should be taken during the race. Sugar (either sucrose or glucose) is easily assimilated and can be recommended. Large quantities, even if rapidly absorbed, may not be immediately available to the muscles and it is best to take small amounts at frequent intervals (50 g. each hour will provide a valuable supplement to the energy available in the body stores). It is also necessary to replace fluid and salt losses in the sweat at regular intervals.

Many distinguished athletes are more than normally sensitive people. The wise trainer will humour their dietary fancies and see that they have the food they like. Individual requirements vary greatly and natural appetite is usually a safe guide.

Chapter 60

EFFECTS OF CLIMATE—DIETS FOR EXPEDITIONS—EMERGENCY RATIONS

CLIMATE

MUCH has been written about the modification of dietary habits considered to be necessary in different climates. Most of this has little scientific background. The effects of climate on the need for nutrients have often been exaggerated. The extra need for water and salt in hot weather is of great importance but, apart from this, climate imposes no important change in the physiological needs.

Water and Salt

In hot climates the body can only be maintained at an even temperature by sweating. The amount of sweat lost will be determined by the environmental temperature, the humidity and the air movement, and also by the amount of physical work done. A man engaged in physical labour in the tropics may readily lose 4 *l.* of sweat a day and under exceptional circumstances double this amount. Sweat contains from 30 to 80 mEq. NaCl/*l.*, the concentration being lower in the acclimatised and trained subject. The body may thus lose 240 mEq. of NaCl each day or about 14 g. of salt. When there is much sweating, it is essential that these losses of water and salt should be made good by increased intakes.

Effects of heat

A classification of the clinical syndromes arising from excessive heat is given in Table 60, 1. This table also shows that excessive heat can be an important cause of illness among merchant seamen and that at least half the cases were attributable to insufficiency of salt and water.

In the ' mild ' cases there is collapse and syncope, which arise from circulatory disorders. The blood supply to the brain and other internal organs is reduced, in part due to a diminished blood volume and in part to an increased blood flow through the skin.

Two syndromes are responsible for the ' severe ' cases. The first is caused directly by salt and water deficiency. As in the mild cases there is evidence of circulatory shock, but the collapse is more marked and there may be vomiting. The muscle cramps characteristic of salt deficiency are frequently present. The output of urine is always greatly diminished and it is of high specific gravity. The diagnostic test is the

TABLE 60, 1. *Classification and incidence of illnesses attributable to heat, treated at the Medical Centre at the port of Kuwait in the Persian Gulf in the summers of* 1956 *and* 1957 (Leithead *et al.*, 1958)

Syndrome	No. of cases
Heatstroke	2
Heat hyperpyrexia	1
Borderline heat hyperpyrexia	5
Heat exhaustion syndromes :—	
‘ Severe ’—	
Salt deficiency with or without heat cramps	59
Anhidrotic heat exhaustion	1
‘ Mild ’—	
Exercise induced heat collapse : heat syncope ; mild water deficiency ; acute heat neurasthenia	60

absence of salt from the urine ; there is no white precipitate of silver chloride on the addition of silver nitrate after acidification with nitric acid.

Anhidrotic heat exhaustion, the second syndrome, is attributable to a failure of the sweat glands to secrete, due to fatigue. This loss of ability to sweat may follow many weeks or months in excessive heat. The rarity of this condition in Kuwait can be attributed to the fact that the merchant seamen had voyages which took them at short intervals to temperate climates where the sweat glands could recover. The principal clinical features are dizziness, palpitations, breathlessness and lack of sleep.

The ‘ dangerous ’ states are heatstroke and heat hyperpyrexia. In the former there may be coma, convulsions or delirium. Leithead *et al.* consider a body temperature over 106° F. (41° C.) as hyperpyrexia, but describe temperatures between 103° and 106° F. (39·5° to 41° C.) as borderline. Heatstroke and heat hyperpyrexia are properly described as dangerous, for even with the best medical care they may prove fatal.

Prevention of the effects of heat.—It is clearly important to reduce exposure as far as possible. Shade and shelter against the sun are obviously desirable. In a ship, as in a factory in the tropics, heat will inevitably be produced by the engines and machinery. These will compete for space with the men, who need cool canteens, rest rooms and a sick bay. In the design of a factory or ship in the tropics a proper compromise between these two essential needs must be effected. It is also important to arrange that no unnecessary physical work is carried out and that, as far as possible, men do not have to work in the midday heat. However, even with the best of management, men will always be exposed to excessive heat and its consequent risks.

It is essential that all exposed men should know these risks and how they can best be avoided. All newcomers to the tropics need some education and must be taught to respect the heat. They must learn that thirst is not always a reliable guide to water requirements, nor is the natural appetite for salt always reliable. Liberal amounts of drinking water must be available not only in the mess and the canteen, but in places of work. It is important to see that this water is cool. While men will readily drink cool water, they may neglect to drink tepid water, even if there is a real physiological need. Each individual can judge whether he is taking enough water from his urine output. If there is not a good flow of urine at least four times in the 24 hours, he is not taking enough. Ample salt must be available on the tables at all meals and men told to use it. Cooks must be instructed to salt the food well. As much as 30 g. of NaCl may be necessary to make good the losses in the sweat, *i.e.* at least double a normal intake. It may be desirable to add salt to the drinking water. Amounts up to 0·1 per cent. are barely perceptible. This is provided by the addition of ½ oz. (2 teaspoonfuls) to the gallon or 25 oz. (one 50-cigarette tin full of ordinary salt) to 50 gal. of water. There is a risk that men may not drink water in which they can taste salt ; provided adequate table salt is available and the men use it, there should be little need to add salt to drinking water.

OTHER NUTRIENTS

The effects of climate on the need for the remaining nutrients are small and unimportant in comparison with the extra need for salt and water in the tropics. They are briefly set out below.

Calories.—The corrections for climate used by FAO in determining national caloric needs and the difficulties in assessing the effects of climate have been discussed in Chapter 2. In considering the caloric requirements of individuals or smaller groups the following points should be considered.

1. Civilised man has developed many and elaborate means of protecting himself against excessive heat and excessive cold. In general this protection is very effective against cold, but much less so against heat.

2. The chief factor determining caloric needs is the amount of physical activity undertaken. This is generally little affected by climate except by extremes of heat or excessive cold. Both of these restrict activity, especially by making active physical recreations unpleasant or impossible.

3. The basal metabolism of the great majority of the natives of the tropics and of most visitors after 6 months residence is about 10 per cent. below European and North American standards. For a man of normal size this means a reduction of about 140 Cal. in the daily needs.

4. There is some indication that the caloric cost of performing a standard task of physical work falls with the rise of environmental temperature, but the evidence is conflicting and the effect, if it exists, is

small and probably negligible. In cold climates, the cost of physical work may be increased by up to 5 per cent. by the 'hobbling' effect of the protective clothing. This may weigh 14 lb. or more and of necessity restricts the ease of movement, besides involving extra energy for carrying it about.

Fat.—When undertaking hard work such as sledging in very cold climates, up to 5000 Cal./day may be needed. If the diet is not to be very bulky, large quantities of fat (up to 250 g. or even more) will be required. As stated in Chapter 6, these large amounts can be digested and absorbed. A high intake of fat is probably essential if hard physical exercise is to be undertaken in any climate.

Protein.—A reduction in the dietary intake of protein in hot climates has often been stated to be desirable, owing to the strain imposed by extra heat liberated by the Specific Dynamic Action of protein. If the dietary intake of protein is 100 g./day, the calories produced by the SDA will not amount to more than 120 a day. This will not seriously disturb the heat balance or cause discomfort. In very hot weather it is unwise to take excessive amounts of meat or other protein-rich foods, but there is no good reason to reduce their intake below what is customary in a mixed diet.

Minerals.—The sweat contains very small amounts of minerals, but the losses of iron may be significant and it has been suggested that this may contribute to the causes of anæmia, which is so common in many countries with hot climates.

Vitamins.—No significant losses occur in the sweat. There is no evidence that the recommended allowances for vitamins need be in any way altered on account of climate. As mentioned in Chapter 31, exposure to cold may precipitate an attack of scurvy. In cold climates it is certainly important to see that intakes of vitamin C in the food are satisfactory. There is, however, no need to increase them above the recommended allowances by giving supplements of ascorbic acid.

Alcohol.—Europeans and Americans working in the tropics are much more prone to alcoholism than at home. This may lead to secondary malnutrition as well as a loss of working efficiency and much domestic unhappiness. Alcohol is readily used as an escape from the irritations, annoyances and discomforts caused by the excessive heat and consequent continual sweating, the plagues of insects, the absence of family and friends, the lack of opportunity for customary sports and recreations and the necessity to work with strange people, whose language is not understood and whose way of life is not fully appreciated. The man or woman in the tropics with a weak personality, unable to make the necessary adjustments in the way of life and to develop new interests, readily falls a victim to alcoholism. Nevertheless, despite its dangers, we would not be without alcohol in the tropics. Taken in moderation, it is a valuable sedative and helps to distract from obsessional attention to duty, and to promote social life. Midday drinking is especially dangerous and the old adage, ‘never drink before sunset,’ is to be recommended. It is also necessary to have the strength of mind to withstand the pressure to have rounds of drinks when in convivial and congenial company.

General Considerations

An adverse climate, whether very hot or very cold, imposes considerable strains, both physical and psychological, on an individual. If the diet is not satisfactory he will be less able to stand these strains. The provision of a satisfactory diet is made difficult by the fact that good supplies of fresh fruit and vegetables are generally not available locally in very cold climates and are usually very limited in very hot dry climates. Modern means of transport, refrigeration and food technology have made it possible to overcome this difficulty, although often at considerable expense.

The importance of good catering and good cooking for men and women who have to live and work in a harsh climate cannot be overstressed. Apart from their effect on physical health, they are immensely important for sustaining morale. The changes imposed by climate in the physiological requirements of nutrients are negligible (the increased requirements for salt and water in hot climates is an exception), compared with the need to provide a good mixed diet and to ensure that it is well cooked and attractively served.

DIETS FOR EXPEDITIONS

Explorers and members of the armed forces frequently have to make expeditions into unknown and hostile country, where the opportunities for obtaining food are either limited or altogether absent. In such circumstances the expedition has to take with it sufficient food for its members. The planning and provision of the rations may make all the difference between the success or failure of the expedition or military operation. An excellent symposium on this subject was held by the Nutrition Society. The report contains accounts of Everest expedition rations (Pugh, 1954), polar rations (Bertram, 1954), rations for tropical expeditions (Platt & Fox, 1954), and British Army operational rations (Smith, 1954).

Members of expeditions are usually active young men. Their requirements for nutrients when on the expedition will be essentially the same as the daily allowances appropriate for men of their class as set out by the Nutrition Committee of the British Medical Association and the Food and Nutrition Board, National Research Council of the U.S.A., and given in full in Chapter 15. The circumstances of an expedition will not raise physiological requirements above these liberal allowances. A practical point is the assessment of probable physical activity and the consequent need for calories. Climbers usually expend between 400 and 600 Cal./hr. with surprisingly little variation (Pugh, 1958). Similar hourly rates of energy expenditure have been found in sledging parties (Masterton *et al.*, 1957). The calorie cost of many other strenuous physical activities is given in a review by Passmore and Durnin (1955) and some of this data has been presented in Table 2. 5 on page 20. The organisers of any expedition have the clear responsibility of estimating the probable daily energy expenditure of the members when in the field and providing rations with the necessary calories.

It is important to see that all members of an expedition have been well fed before the expedition sets out. This will ensure the presence of sufficient stores of the nutrients normally carried by the body and discussed in the appropriate chapters in Part I. The size of these stores varies for different nutrients. While they enable a man to survive for a long time with intakes of nutrients far below the daily recommended allowances, this is only at the expense of some loss of physical fitness and powers of mental concentration. Even a very short period of undernutrition (as little as 24 hours) may reduce significantly a man's ability to carry out a hard and difficult task. This particularly applies to deprivation of calories.

Further, there is no evidence that any period of previous training will prevent such physiological deterioration. In particular no previous training can prevent the dehydration and consequent deterioration that follow rapidly upon a reduction in the fluid intake below the physiological losses. It is impossible to train oneself to do without water. Nevertheless, in some circumstances it may be a valuable experience for members of an expedition to live for a few days on an inadequate diet and with a reduced fluid intake, for it will provide an opportunity for the men to feel the adverse effects on themselves of such deprivations. This experience may enable them to adjust their plans sensibly in a crisis. Fit young men frequently overestimate their ' toughness ' and ability to carry on in a crisis. Such over-confidence may be disastrous both for themselves and those for whom they may be responsible. The importance of an adequate water supply for expeditions cannot be overstressed. On Sir John Hunt's successful assault on Everest great care was taken to see that all members of the expedition drank sufficient water. This may have been one of the factors responsible for their success.

After assessing the physiological needs for nutrients, the organisers of an expedition have to translate these into terms of food and then to arrange for the supply of the food. A first consideration is an estimate of the extent to which an expedition can ' live off the country.' In practice, this is negligible on high mountains and near the North or South Poles, and very limited in deserts and sub-Arctic regions. But in tropical and sub-tropical regions there is usually game which can be trapped or shot, and often natives from whom grain can be purchased. It is always a wise precaution to see that members of an expedition have the necessary equipment for fishing, trapping or shooting and the skill to use them in an emergency. It is well known that Arctic expeditions have perished for lack of such equipment and skill under conditions in which the Eskimos have survived.

In most expeditions the major portion of the food has to be carried with the party. It is clearly important to reduce the load to be carried—no matter whether the means of transport are aeroplanes, trucks, pack animals, porters or members of the expedition. Modern food technology has contributed enormously to this problem. Meat, fruit and vegetables can be prepared so that only the edible portions are packed and no waste is carried. Great improvements have been made in the quality of dehydrated foods. Packing materials and methods have also improved, so that packages can be made which will stand up without damage to rough handling and which endure long storage in any climate without deterioration of the contents. In these ways it has been possible to reduce the weight of stores. It is also important to arrange the packing so that the food can be easily distributed and, if necessary, divided up into smaller units for small parties.

The food must be provided in a form so that meals can be prepared with a minimum of cooking and served as attractively as possible. As many members of an expedition as possible should have some training in cookery.

The armed forces of several countries have expended much effort in devising rations suitable for small parties of varying size and also individual rations. The experience gained in the last 20 years has revolutionised the diet provided for the soldier during active operations. Smith (1954) has given a good account of the British Army's operational rations which were in use in 1954. Table 60, 2 gives a Mountain (Arctic) Pack Ration in use by the British Army in 1954. The ration is sufficient for two men for one day or for one man for two days. It was packed in a cylindrical tin and weighed 6 lb. 11 oz. The dehydrated and tinned foods provided about 10,000 Cal. Modifications and improvements in design are being continually investigated.

EMERGENCY RATIONS

Lifeboats have for long been provided with rations for those who survive the immediate disaster of shipwreck. Many civilian and military aeroplanes also carry emergency rations for use in the event of a forced landing in an isolated place. In some military planes the pilot can, in an emergency, eject himself and his seat from the plane and descend by parachute. Attached to the undersurface of the seat are rations and equipment for survival. There has been much study in recent years of the most suitable type of emergency ration for these and other purposes (Hervey & McCance, 1954).

Castaways are usually rescued, if at all, within a period of 14 days. It is not generally considered practical to plan for any longer period of survival. Rescue equipment must provide many other things besides

TABLE 60, 2. *The Mountain (Arctic) Pack Ration (for two men for one day)*

Items	Number and Weight
Pemmican	2 × 4 oz. slab
Tea, sugar and milk powder	1 × 5 oz. tin
Biscuits, sweet, service	2 × 8 oz. packet
Chocolate, raisin	6 × 2 oz. bars
Boiled sweets	4 oz.
Cheese	1 × 9 oz. tin
Margarine	1 × 4 oz. tin
Sugar	2 × 2 oz. plaquettes
Salt	2 × ½ oz. packets
Bacon, chopped	1 × 8 oz. tin
Rolled oats	1 × 4½ oz. tin
Ascorbic acid	4 tablets in a tin
Flare matches	6 matches in a packet
Fuel (starter)—for Primus stove	4 tablets in carton
Latrine paper	12 pieces

(From *Manual of Army Health*, 1954)

food and, in selecting what articles to include, it is necessary to keep the total bulk of the supplies to a minimum. Food, in fact, receives a very low priority: for no healthy man will die of starvation in 14 days; nor will he suffer any permanent adverse effect from the experience, although his physical efficiency will be somewhat reduced at the time. However, within 14 days he can readily die of lack of water or from exposure to extremes of heat or cold. Protection against the environment and water have, therefore, priority over food, as also has radio equipment which enables the survivor to get in touch with rescue parties. Nevertheless all emergency equipment contains some food which will, in part, prevent the physical deterioration consequent upon total fasting and, perhaps more important, sustain the morale of the survivors. Before discussing these rations it is proper to discuss the more essential problem of water supply.

Minimum water requirements

A man at rest in an equable climate loses at least 800 ml. of water daily by evaporation from the skin and lungs. This may be increased fourfold or more by the necessity to do hard physical work or in a hot environment. The minimum amount of water that his kidneys must pass is a little less than 400 ml. daily. Against these essential losses may be offset the metabolic water produced by the oxidation of carbohydrate, protein and fat in the tissues. Under conditions of fasting and rest this amounts to about 200 ml. daily. Thus to prevent a loss of body water, the minimum daily intake must be 1 *l.*, but much more is needed if physical work is undertaken or the weather hot. As stated in Chapter 1, the body of a healthy man contains about 40 *l.* of water. A loss of 2 *l.* or more will usually cause discomfort and inefficiency, a loss of 4 *l.* will be disabling and a loss of 8 *l.* will rapidly lead to death. Thus even with everything else in their favour, few men would survive 10 days without water.

It is rarely possible to provide emergency water which would be sufficient to cover the losses that might arise under very hot conditions. Small solar stills have been designed which can meet in part the extra needs of castaways on a tropical sea. In such conditions it is essential to attempt to minimise water losses by the provision of tents or other material which will give shade; survivors must be warned of the adverse effects of unnecessary physical activity. In great heat, sea water can be used to keep the body cool.

The danger of drinking sea water.—Sea water has a concentration of sodium ions of 420 mEq./*l.* and of chloride ions 470 mEq./*l.* The corresponding concentrations in the blood plasma are about 142 and 104. Sea water is thus much more concentrated than the body fluids. Moreover, the human kidney is not normally able to concentrate either sodium or chloride to as high a level as in the sea (Hervey & McCance, 1952). Experiments in which *small* quantities of sea water have been drunk have given equivocal results. There may be some temporary retention of water, but this is associated with an increased tonicity of the body fluids. This may be expected to give rise to an osmotic diuresis in a short time in which the water retained will be lost. In experimental studies on man, it has proved very difficult to demonstrate either a beneficial or an adverse effect of drinking small quantities up to ½ pint (250 ml.) of sea water. The heroic experiments of Bombard (1953) showed only that one man could drink a lot of sea water and survive. Critchley (1943), however, studied carefully the records of castaways during the Second World War and showed that the drinking of large amounts of sea water was always fatal. It is probably wise to forbid the drinking of any sea water.

The composition of emergency rations

The first consideration is that the salt intake should be as low as possible, for the necessity to excrete salt will increase the need for water. Proteins also produce nitrogenous end-products which require water for their elimination and so it is desirable that the protein intake should not be high. Deprivation of protein for a temporary period of 14 days will cause no harm, nor will a similar temporary restriction of the intake of minerals and vitamins. Emergency rations have been devised in which the foods are restricted to a mixture of carbohydrate and fats which can be made up in sweets and toffees. Fat has the advantage over carbohydrate that it provides over twice the amount of calories for a given unit of weight. The more fat in the rations, the less will be their bulk. On the other hand, dietary carbohydrate is more effective than fat in

' sparing ' endogenous nitrogen metabolism and so will reduce the loss of body protein and also the urine volume. Carbohydrate will also prevent the ketosis that arises when an excess of fat is metabolised. Johnson and Sargent (1958) carried out on a large scale realistic field trials of various emergency rations in different climates for periods of 14 days. In many of these trials the daily water intake was limited to 900 ml. Their results indicated that men stood up to survival conditions best if provided with an emergency ration in which the proteins, carbohydrates and fats were distributed in the normal manner (15 per cent. of calories from protein, 52 per cent. from carbohydrate and 33 per cent. from fat).

Whatever the nature of the ration, it is essential that it be provided in a compact form, that requires no cooking or other preparation and that it does not deteriorate on storage even under adverse conditions. Various forms of boiled sweets, candies, toffees and meat bars can be used for this purpose.

APPENDIX

DIETS

The diet sheets that follow have been constructed to illustrate the quantitative and qualitative aspects of diets required for the treatment of various diseases. The quantities given in a standard diet sheet will obviously require some modification in relation to the size, age, sex and occupation of the patient. In the dietetic treatment of most diseases it is unnecessary to weigh accurately the amounts of the different foods eaten. Under these circumstances sufficient accuracy will be secured by the use of the terms ‘ small,’ ‘ medium ’ or ‘ large helping.’ A small helping weighs approximately 1 to 2 oz., a medium helping 2 to 3 oz. and a large helping 4 oz. or more.

DIET No. 1

LOW CALORIC DIET

suitable for

OBESITY

Approximately : Protein 60 g., Carbohydrate 100 g., Fat 40 g., Cal. 1000.

Breakfast	Piece of fruit (fresh or stewed, no sugar), *or* small glass of fruit juice. 1 egg, *or* 2 rashers of lean bacon (grilled and drained of fat), *or* small piece of white or smoked fish. 1 thin slice of bread.* Butter and milk from allowance.† Tea *or* coffee (no sugar).
Mid-morning	Tea *or* coffee, milk from allowance (no sugar).
Dinner	Clear soup or cup of meat, vegetable or yeast extract. Medium helping of lean meat, poultry, game, lean ham, tongue, liver, kidney, tripe, *or* white or smoked fish. Large helping of any kind of vegetables except potatoes, peas, beans, lentils and sweet corn. Piece of fruit (fresh or stewed, no sugar). Tea *or* coffee—milk from allowance if desired.
Tea	1 thin slice of bread. Salad vegetables and tomatoes if desired. Butter and milk from allowance. Tea.
Supper	Small helping of white fish, *or* 1 egg, *or* small piece of cheese, *or* small helping of very lean meat. Salad or other vegetables as desired. 1 thin slice of bread. Piece of fruit (fresh or stewed, no sugar). Butter and milk from allowance. Tea *or* coffee.

† *Allowance for day :* ½ pint (0·25 *l.*) skimmed milk (use of whole milk increases diet to 1100 Cal.).
¾ oz. (22 g.) butter *or* margarine (to include any fat used in cooking).

* *Instead of* 1 *thin slice of bread the following may be taken :*
2 crispbreads,
or 2 plain biscuits, *e.g.* rich tea,
or 3 water or cream cracker biscuits,
or 2 oatcakes.

Foods to be avoided :

Sugar, glucose, sweets, chocolate, jam, marmalade, honey, cakes, buns, scones, potatoes, pastry, pies, porridge, puddings, thickened gravy, sauces, cream, ice-cream, tinned and dried fruit, thickened tinned or packet soups, fried food and food cooked with flour or sugar ; also beer, stout, heavy wines and spirits.

Management :

If it is desired to increase or decrease the value of the diet in respect of proteins, carbohydrates, fats or calories, the exchange lists given for diabetic diets (p. 847) may be used.

Saccharine may be used for sweetening.

Meals may be rearranged to suit the patient's preferences.

DIET No. 2

SEMI-FLUID LOW-ROUGHAGE DIET

suitable for patients who have

DIFFICULTY IN CHEWING OR SWALLOWING, OR WHO ARE SEVERELY ILL WITH ULCERATIVE OR MALIGNANT DISEASE OF THE ALIMENTARY TRACT

Approximately : Protein 90 g., Carbohydrate 270 g., Fat 120 g., Cal. 2500.

Early morning	Fruit juice with sugar.
8 A.M.	Strained porridge with milk from allowance * *or* cream. Coffee with fortified milk or cream and sugar from allowance.
10 A.M.	Fortified milk *or* some proprietary preparation of milk, *e.g.* Benger's Food, Horlicks, Ovaltine.
12 NOON	Strained cream soup. Savoury custard—using cheese, very finely minced chicken, ham, pounded white or smoked fish, *or* scrambled eggs *or* omelette.
2 P.M.	Sweet made with puréed fruit, cream and sugar, *or* small helping of mousse or cold soufflé, *or* ice-cream with fruit, chocolate or butter-scotch sauce, *or* jelly made with fruit juice, gelatine and sugar—served with cream.
4 P.M.	Coffee made with fortified milk or cream and sugar from allowance, *or* fortified milk flavoured with yeast or vegetable extract.
6 P.M.	Milk pudding with puréed fruit *or* sweet as at 2 P.M.
8 P.M.	Savoury custard as at lunch *or* scrambled or poached egg *or* omelette. Coffee with milk or cream and sugar from allowance.
10 P.M.	Proprietary preparation of milk *or* cocoa *or* chocolate and fortified milk.

* *Allowance for day :* 1 pint (0·5 *l.*) of whole milk.
1 pint (0·5 *l.*) of whole milk fortified with 2 oz. (60 g.) of full cream dried milk powder.
3 oz. (90 g.) sugar, or more if desired.

Management :

When necessary, the calories can be increased by adding more cream, butter or sugar. Fruit juice with sugar or glucose to drink as desired.

DIET No. 3

BLAND DIET, LOW IN ROUGHAGE

suitable for patients with

All Types of Dyspepsia
Irritable Bowel
Nervous Diarrhœa

Breakfast	Cereal, small helping (if desired). 1 or 2 eggs, lightly boiled, poached or scrambled. Crisp toast *or* rusks, and butter *or* margarine and jelly. Weak tea *or* coffee.
Dinner	Boiled or steamed white fish, *or* sweetbreads *or* tripe. Mashed potatoes, puréed vegetable. Milk pudding.
Tea	Toast, biscuits *or* rusks. Butter *or* margarine, honey *or* jelly. Sponge cake. Weak tea.
Supper	Milk or strained vegetable soup. Breast of chicken, rabbit, *or* tender beef or lamb. Baked potato, puréed vegetables. Stewed apples *or* fruit jelly, with milk or cream.

Before bed a glass of warm milk or a proprietary milk preparation.
Fruit juice with water should be taken with or between meals.

Instructions for a Patient with Dyspepsia

1. Take four meals a day.
2. Take your meals at regular times daily.
3. Eat your meals slowly ; chew your food carefully.
4. Avoid rush and hurry before and after meals. If possible rest for a few minutes before and after eating.
5. See that you get sufficient sleep at night.
6. Remember that anxiety and worry can upset digestion.
7. Avoid large, heavy meals, fried foods, and any article of food which you find disagrees with you.
8. Avoid foods which are mechanically irritating or chemically stimulating (see list below), and very hot or very cold foods.
9. Do not smoke or drink alcohol before meals, when the stomach is empty.
10. Drink only sparingly at meals for this will help to ensure proper mastication ; but drink plenty of water between meals.
11. Consult your dentist at regular intervals.

The following foods should be avoided during the acute stage of dyspepsia, and taken sparingly during intermissions by those liable to frequent attacks of dyspepsia. For those who suffer from dyspepsia only occasionally, no special restrictions may be necessary ; by **trial and error** the patient can find out which of the articles listed below should be avoided :—

1. Alcohol, strong tea and coffee, gravies and soups made from meat extracts.
2. Raw vegetables, celery, cucumber, onions, radishes, watercress, tomatoes, mushrooms.
3. Raw unripe fruit and dried fruit (*e.g.* currants, raisins and figs), nuts, and the pips, skins and peel of all fruits, whether cooked or in puddings, cakes or jam.
4. Pickles, spices and condiments.
5. Tough, twice-cooked, or highly seasoned meats, including sausages, bacon and pork.

6. Fried fish, and fatty fish such as herring, kipper, mackerel, salmon and sardines.
7. Rich and heavy puddings.
8. All fried foods.
9. New bread and scones, hot buttered toast, wholemeal bread or biscuits, rye or wheat crispbread, coarse cereals, pastry, cakes containing dried fruit or peel.

The following foods are permitted :—

1. Weak tea or coffee.
2. Dairy products, *i.e.* milk, cream, butter, cream cheese, eggs (not fried).
3. Fish—white fish, steamed, baked or boiled.
4. Meat—sweetbreads, brains, tripe, chicken, rabbit, lean ham, tender beef, mutton or lamb.
5. Crisp toast (buttered cold), rusks and white bread (not new).
6. Plain biscuits and cakes, or sponge cake. Honey, golden syrup, jellies.
7. Cereals—refined and well cooked, *e.g.* cornflour, semolina, ground rice and oatflour porridge.
8. Puddings—junket, jellies, custards, blancmange, soufflé, mousse.
9. Vegetables—potatoes, boiled and baked, and green and yellow vegetables finely sieved and puréed with butter.
10. Fruits—stewed and finely sieved, and served as purées or fools, and fruit juices strained, sweetened, and diluted with water, or used in jellies.

DIET No. 4

BLAND DIET, LOW IN ROUGHAGE

suitable for patients who have

A Peptic Ulcer or any Inflammatory, Irritative or Malignant Disease of the Alimentary Tract with Symptoms of Moderate Severity

On waking	Glass of milk *or* weak tea—milk and sugar if desired. Biscuit *or* ½ slice of crisp toast, buttered when cold.
Breakfast	Strained porridge with milk from allowance * *or* small helping of crisp cereal (avoiding those containing bran, nuts or fruit) with puréed fruit or fruit juice *or* milk from allowance. 1 egg *or* small piece of white fish. Crisp toast buttered when cold *or* buttered bread at least 24 hours old. Jelly marmalade *or* run honey *or* golden syrup. Weak tea *or* coffee with milk and sugar if desired.
Mid-morning	Glass of milk *or* milk drink. Biscuit.
Dinner	Strained cream soup, if desired. Small helping of fish *or* lean tender meat. Sieved vegetables. Potatoes, mashed or creamed, *or* crisp toast. Milk pudding with sieved fruit *or* jelly made with fresh fruit juice *or* fruit fool *or* soufflé *or* mousse with cream.
Tea	Crisp toast, buttered when cold, *or* bread (not new) may be made into sandwiches using sieved hard-boiled egg, scrambled egg, finely minced chicken or ham or cream cheese. Jelly, *or* run honey, *or* golden syrup. Plain sponge or madeira cake *or* biscuits. Weak tea with milk and sugar as desired.
Supper	Egg *or* creamed or grated cheese *or* meat *or* fish, as at dinner. Sieved vegetable, if desired. Small helping of milk pudding with puréed fruit, *or* puréed fruit with biscuits *or* sweet as at dinner. Bread and butter *or* crisp toast may be substituted for sweet. Weak tea *or* coffee with milk and sugar, if desired.
Bedtime	Milk drink and biscuits.

* *Allowance for day :* 2 pints (1 *l.*) milk.

Management :

The foods that are best avoided and those that are usually suitable are given in the lists on pages 824-825.

DIET No. 5

HIGH PROTEIN, LOW FAT DIET

suitable for patients who have

Chronic Pancreatic Insufficiency[1]
Tropical Sprue[1]
Idiopathic Steatorrhœa[2]

Approximately : Protein 120 g., Carbohydrate 350 g., Fat 45 g., Cal. 2300.

Breakfast	Helping of cereal with fresh or stewed fruit *or* fruit juice *or* milk from allowance.* 1 egg *or* 2 rashers of lean bacon, grilled and drained of fat, *or* piece of white fish. Crisp toast *or* bread. Jelly marmalade, honey *or* syrup. Tea *or* coffee with milk and sugar from allowance.
Mid-morning	Cup of coffee *or* milk drink with milk and sugar.
Dinner	Tomato *or* fruit juice *or* extracts of yeast, meat or vegetables. Large helping of lean meat *or* white fish. Helping of sieved vegetables (see below). Potatoes, boiled, mashed or baked. Fruit, fresh, tinned, stewed or made into jelly *or* whipped with egg white. Milk pudding with milk from allowance. Tea *or* coffee with milk and sugar.
Tea	Sandwiches with filling of egg, chicken, lean ham, cheese or lean meat. Tea with milk and sugar.
Supper	Large helping of lean meat or fish. Vegetables, if desired. Potato. Helping of milk pudding with fruit, *or* bread with jam, honey or syrup. Tea *or* coffee with milk and sugar.
Bedtime	Milk drink using milk from allowance. 1 plain biscuit.

* *Allowance for day :* 2 pints (1 *l.*) of skimmed milk.
2 oz. (60 g.) sugar, more if desired to increase calories.

[1] In those cases of the sprue syndrome and chronic pancreatitis in which acid frothy stools indicate an intolerance to starch, the amount of starchy foods (porridge, bread, cereal products and potatoes) in Diet No. 5 should be reduced.

[2] Cœliac disease is not classed as "idiopathic" since it is known to be due to idiosyncrasy to gluten. In this disease bread or other wheat or rye products must be avoided entirely.

Management :

Foods to be avoided.—Butter, margarine, lard, dripping, cooking fat, fat of meat, tinned meat or fatty fish ; foods incorporating fat in cooking, *e.g.* pastry, suet puddings, cakes, sauces, soups, fried food ; cream, ice-cream, nuts, chocolate, caramels, toffee.

Foods suitable.—Sugar, boiled sweets, fruit, jam, marmalade, honey, syrup, jelly. Very lean meat—except pork ; poultry—except goose and duck ; liver, kidney, tripe, heart, rabbit, hare, very lean ham, white or smoked fish. Egg—boiled, poached or baked, or made into custard with skimmed milk. Cheese—not cream cheese. Finely sieved vegetables, flower of cauliflower, tomato without skins or pips, asparagus tips. Sauce may be made for meat, fish or vegetables with skimmed milk, flour, and grated cheese, hard-boiled egg or parsley. **No** fat to be used.

DIET No. 6

A SAMPLE GLUTEN-FREE MENU

suitable for patients with

CŒLIAC DISEASE

Breakfast	Fruit as desired. Cornflakes *or* puffed rice *or* porridge, with milk. Egg with bacon *or* ham. Gluten-free bread with butter and marmalade. Tea *or* coffee with sugar and milk.
Mid-morning	Tea *or* coffee with milk and sugar. Gluten-free biscuits.
Dinner	Soup made with meat or vegetable stock and thickened with gluten-free flour. Rice, barley, sago, potatoes, peas and lentils may be added. Meat *or* fish as desired—any gravy to be thickened with cornflour or gluten-free flour. Vegetables, avoiding those prepared with mayonnaise or sauce, *e.g.* baked beans. Potatoes. Puddings—if flour required, use gluten-free flour. Avoid custard powder, semolina, farola, and packets or tins of pudding mixture. Special varieties of ice-cream are permissible. Fruit.
Tea	Sandwiches made with gluten-free bread, gluten-free scones, cakes and biscuits. Jam, jelly *or* honey. Tea with sugar and milk.
Supper	Meat or fish dish, as for dinner, *or* egg or cheese dish. Vegetables as desired. Gluten-free bread, scone, cake or biscuit *or* pudding as at dinner. Butter and milk as desired. Tea *or* coffee with sugar and milk.
Bedtime	Milk, tea *or* coffee *or* meat or vegetable extract. Gluten-free biscuits.

Management :

Avoid wheat, flour, all foods containing flour, *e.g.* bread, cakes, scones, biscuits, tinned and packet soups, tinned meat, macaroni, spaghetti, semolina, farola, wheat flakes, puffed wheat, sausages, baked beans, pastry, pies, made up dishes and food dressed with breadcrumbs.

Recipes

Bread, scones and small cakes can be made from gluten-free wheat starch. The following recipes are recommended :—

Gluten-free bread :

12 oz. of wheat starch.
1 oz. yeast.
½ oz. cooking fat.
1 teaspoon of sugar.
1 teaspoon of salt.
8 oz. milk.
4 oz. boiling water.

Mix the salt and wheat starch and rub in fat. Cream together the sugar and yeast with a little of the warm milk-and-water mixture. Stir this into remaining liquid, and then add all the liquids to the starch and salt. Mix until smooth ; cover and stand in warm atmosphere (70° to 80° F.) for 20 minutes.

Place in greased bread tin.

Place in oven which has been pre-heated to 420° F. (Reg. 6) and bake for 20 minutes when loaves will have set. Remove bread from tin, place on wire cooking tray and replace in oven until lightly coloured.

Loaf or scone :

½ lb. wheat starch.
2 oz. margarine or butter.
4 level teaspoons of baking-powder.
½ pint milk.
½ teaspoon of salt.

Sieve dry ingredients and rub in fat. Make well in centre and add sufficient milk to make a very soft dough. Turn into a greased shallow tin. Bake for approximately 30 minutes at 450° F. (Reg. 7).

Small cakes :

6 oz. wheat starch.
4 oz. icing sugar.
4 oz. margarine or butter.
1 teaspoon of baking-powder.
1 egg.
Milk if necessary.

Cream fat and sugar. Add beaten egg. Gradually fold in wheat starch and baking-powder. Mix to soft consistency with milk. Bake in greased patty tins in moderate oven, 400° F. (Reg. 5) for 15 to 20 minutes.

May be flavoured with lemon, orange juice, vanilla or almond essence ; dried fruit may be added.

DIET No. 7

HIGH ROUGHAGE, HIGH FAT

suitable for patients with

Atonic Constipation who are Normal or Less than Normal in Weight

Early morning	Glass of hot water.
Breakfast	Porridge with cream or milk, *or* bran cereal with stewed fruit, dried or fresh. Egg, bacon, sausage, liver *or* fish—may be served with tomato or potatoes. Wholemeal bread, may be toasted, *or* oatcakes *or* bran scone—buttered liberally. Thick marmalade *or* jam. Tea *or* coffee with milk and sugar as desired.
Mid-morning	Yeast, meat or vegetable extract, *or* glass of milk, tea *or* coffee.
Dinner	Vegetable soup, including plenty of chopped fresh vegetables, dried peas and beans, lentils and barley. Helping of any kind of meat *or* fish. Large helping of vegetables ; include raw salads frequently. Potatoes. Fresh or stewed fruit *or* pudding made with dried fruit or nuts *or* suet pudding *or* tarts—may be served with cream. Oatcakes with cheese. Tea *or* coffee.
Tea	Sandwiches made with wholemeal bread and filling of dates, date and walnut, apple and walnut, cheese and apple, lettuce, tomato, cucumber or cress, *or* wholemeal bread, liberally buttered, with thick jam or comb honey. Gingerbread, fruit cakes or other cakes and biscuits incorporating dried fruit, nuts or coconut. Tea.
Supper	Helping of any kind of meat *or* fish. Large helping of vegetable *or* salad. Wholemeal bread *or* oatcake *or* wholemeal scone—liberally buttered—cheese *or* jam if desired. Fruit, fresh or stewed. Tea *or* coffee.
Bedtime	Glass of hot water.
Take liberally	Vegetables—particularly raw salads and coarse green vegetables. Fruit, fresh or raw, and nuts. Water.

DIET No. 8

VERY LOW FAT, HIGH CARBOHYDRATE DIET

suitable for patients with

ACUTE PARENCHYMAL DISEASE OF THE LIVER DUE TO TOXIC OR INFECTIVE AGENTS
SEVERE OBSTRUCTIVE JAUNDICE

Approximately : Protein 80 g., Carbohydrate 400 g., Fat 20 g., Cal. 2100.

Early morning	Glass of fruit juice, with glucose *or* sugar.
Breakfast	Strained porridge *or* breakfast cereal with milk from allowance.* 1 slice of bread—may be toasted. Jelly marmalade *or* honey. Tea with milk and sugar from allowance.
Mid-morning	Glass of fruit juice with sugar *or* coffee made with milk from allowance.
Dinner	Small helping of very lean tender meat, poultry, liver, sweetbreads, tripe, lean ham *or* white or smoked fish. Small helping of sieved vegetables. Helping of mashed potato. Cereal pudding made with milk from allowance. Fruit—fresh, stewed or tinned.
Tea	2 thin slices of bread *or* plain biscuits. Jam, jelly *or* honey. Tea with milk and sugar.
Supper	2 thin slices of bread *or* plain biscuits. Jam, jelly *or* honey. Cereal pudding made with milk from allowance. Fruit—fresh, stewed or tinned. Tea *or* coffee with milk and sugar.
Bedtime	Milk drink *or* fruit juice with sugar.

* *Allowance for day :* ½ pint (0·25 *l.*) of skimmed milk—for use in tea.
1 pint (0·5 *l.*) of skimmed milk with 2 oz. dried skimmed milk powder.
2 oz. (60 g.) sugar, or more if desired.

Management :

Take liberally fruit juice with sugar or glucose throughout day.

Avoid.—Butter, margarine, dripping, cooking fat, lard and any foods including them. Fat of meat, fatty meat such as goose, duck or pork—bacon or tinned meat. Fatty fish such as herring, kippers, bloaters, mackerel, sardines and pilchards or salmon. Oils, cream, egg yolk, salad cream, ice-cream, sauces made with fat. Pastry, pies, puddings other than milk pudding. Cakes, chocolates, sweets containing fat such as toffee, fudge or tablet. Fried foods and the use of fat in cooking.

DIET No. 9

LOW FAT, HIGH CARBOHYDRATE DIET

suitable for patients with

SUBACUTE PARENCHYMAL DISEASE OF THE LIVER (SUBACUTE HEPATITIS)
OF MODERATE SEVERITY
SEVERE OBSTRUCTIVE JAUNDICE (RECOVERING)

Approximately : Protein 110 g., Carbohydrate 400 g., Fat 50 g., Cal. 2500.

Early morning	Fruit juice with sugar *or* glucose.
Breakfast	Porridge *or* cereal *or* stewed fruit with milk from allowance * *or* fruit juice. 2 slices of bread—may be toasted. Marmalade *or* honey. Tea *or* coffee with milk and sugar.
Mid-morning	Glass of fruit juice *or* tea *or* coffee with milk and sugar. Plain biscuit.
Dinner	Medium helping of lean meat, poultry, liver, kidney, tripe, sweetbreads, *or* white or smoked fish. Helping of sieved vegetables *or* flower of cauliflower *or* skinned tomato *or* asparagus tips. Helping of potatoes. Cereal pudding, made with milk. Fruit—fresh, stewed or tinned.
Tea	2 slices of bread—may be toasted, *or* plain biscuits. Jam, jelly *or* honey. Tea with milk and sugar.
Supper	Medium helping of meat *or* fish as at dinner. Sieved vegetable if desired. 2 slices of bread—may be toasted. Jam, jelly *or* honey. Tea *or* coffee, with milk and sugar.
Bedtime	Milk drink *or* fruit juice with sugar *or* glucose.

* *Allowance for day :* ½ pint (0·25 *l.*) of whole milk—for use in tea.
1 pint (0·5 *l.*) of skimmed milk with 2 oz. of dried skimmed milk powder.
½ oz. (15 g.) butter *or* margarine.
Sugar—2 oz. (60 g.)—or more if desired.

Management :

As for Diet No. 8.

DIET No. 10

HIGH PROTEIN, MODERATE FAT DIET

suitable for patients with

SUBACUTE PARENCHYMAL DISEASE OF THE LIVER (CONVALESCENT)
CIRRHOSIS OF THE LIVER WITHOUT JAUNDICE

Approximately : Protein 120 g., Carbohydrate 360 g., Fat 105 g., Cal. 2900.

Early morning	Tea with milk from allowance *—sugar if desired—*or* fruit juice with glucose.
Breakfast	Porridge *or* cereal *or* stewed fruit with milk from allowance, *or* fruit juice. Lean bacon—grilled and drained of fat, *or* egg—poached, boiled or scrambled, *or* piece of fish. Bread—may be toasted. Marmalade *or* honey. Butter and milk from allowance. Tea *or* coffee with milk.
Mid-morning	Tea, coffee *or* milk drink. Plain biscuit.
Dinner	Large helping of lean meat, poultry, game, liver, kidney, tripe, sweetbreads, lean ham, *or* white or smoked fish. Helping of vegetables. Helping of potato—boiled, mashed or baked. Light sweet, incorporating egg if possible. Fruit—fresh, stewed or tinned. 2 plain biscuits with cheese.
Tea	Sandwiches with filling of scrambled or sieved hard-boiled egg, cheese, minced meat, chicken *or* ham. Small piece of plain cake *or* plain biscuits. Tea with milk.
Supper	Average helping of meat as at dinner, *or* egg with lean bacon, *or* cheese *or* 2 eggs scrambled. Vegetables if desired. Bread with butter and jam, jelly *or* honey, *or* milk pudding with fruit. Tea *or* coffee with milk.
Bedtime	Milk drink. Plain biscuit.

* *Allowance for day :* 1 pint (1 *l.*) of milk.
1 oz. (30 g.) of butter or margarine.

Management :

Avoid fried food, fat in excess of allowance, pastry, pies, puddings including much fat, such as suet puddings and dumpling.

DIET No. 11

MODERATE FAT DIET

suitable for patients with

CHRONIC CHOLECYSTITIS (WITHOUT OBESITY)

Approximately : Protein 90 g., Carbohydrate 380 g., Fat 70 g., Cal. 2510.

Early morning	Glass of water, hot or cold.
Breakfast	4 to 5 tablespoonfuls porridge (unless there is flatulence), *or* average helping cornflakes. Milk from allowance.* Small helping white fish, steamed or baked, with small helping tomato, *or* cold lean ham—all visible fat removed ; 1 egg, if tolerated. 2 thin slices bread as crisp toast. Butter *or* margarine from allowance. Jelly marmalade. Tea with milk and sugar.
Mid-morning	Fruit juice *or* cup of tea. Sugar from allowance. } Glass of water, hot or cold.
Dinner	Clear soup *or* cup of meat, vegetable or yeast extract. Small helping lean meat, *or* rabbit, mutton, tripe *or* poultry. Sieved vegetables. (If flatulence, avoid cabbage, sprouts, stalk of cauliflower, peas, onion, turnip.) Average helping potato *or* crisp toast. Small helping milk pudding. Stewed or fresh fruit.
Tea	1½ thin slices bread *or* plain biscuit. Honey *or* jam. Banana *or* other fruit. Tea with milk and sugar.
Supper	Small helping white fish *or* 1 egg plus 1 oz. (30 g.) cheese. Small helping salad—tender lettuce leaves, tomato, cress. 3 thin slices bread *or* crisp toast. Honey *or* jam. Tea with milk and sugar.
Bedtime	Glass of hot water.

* *Allowance for day :* Milk, whole, 1 pint (0·5 *l.*).
Butter *or* margarine, 1 oz. (30 g.).
Sugar, 2 oz. (60 g.).

Management :

If flatulence is present, suitable vegetables are : tomato, marrow, flower of cauliflower, asparagus, carrot, spinach.

Avoid—Fried foods and foods baked in fat such as Yorkshire pudding. Foods made with much butter and eggs, suet puddings, pies and pastries. Highly seasoned foods. Pork, duck, goose, salmon, herring, and fat of meat. Brains, sweetbread, kidney, liver, and fish roe. Strong tea and coffee, and alcohol.

Take plenty of fluid between meals.

DIET No. 12A

VEGETABLE OIL * DIET, HIGH IN CALORIES

suitable for patients who are underweight

Calories 3000 or more. Animal fat less than 15 per cent. of Calories.
Vegetable fat approximately 20 per cent. of Calories.

Food allowed in limited quantities :

Milk, ½ pint.
Vegetable oil, 2½ oz. (5 tablespoonfuls), to be used for cooking or as salad dressing. If used for frying, put double the quantity into pan since some will remain unconsumed after cooking. Do not heat oil for frying more than twice.
1 egg plus ¾ oz. cheese or 2 eggs or 1½ oz. cheese.

Food allowed in unlimited quantities :

Bread, rolls, plain cookies, scones made without fat.
Meat of any description except those listed below, avoid visible fat.
Fish, all varieties.
Fruit.
Vegetables.
Potatoes.
Jam, marmalade, honey, syrup.
Sugar.
Sweets except chocolate, tablet and fudge.
Puddings, made with milk from allowance.
Biscuits, avoid cream, chocolate and fancy varieties.
Sauces, made with oil and milk from allowance.
Cereals including breakfast cereals.
Porridge.
Soups, any vegetable soup, but if made from meat stock skim off fat, avoid cream soups.
Meat extracts and vegetable extracts.
Tea and coffee, milk from allowance.

Foods to be avoided :

Fats, including butter, margarine, dripping, lard, cooking fat, fat of meat, bacon and ham.
Fatty meat, pork, goose, duck, tongue and all tinned meat and sausages.
Cream, ice-cream.
Chocolate and sweets made with fat, such as caramel, fudge and tablet.
All foods made with fat such as cakes and puddings except those home-made with vegetable oils.

* A variety of oils may be used, but not olive oil or coconut oil. Suitable commercial preparations readily available in Great Britain are 'Mazola' oil and 'Twirl.'

DIET No. 12B

VEGETABLE OIL DIET, LOW IN CALORIES

suitable for patients leading sedentary lives

Approximately: Protein 75 g., Carbohydrate 270 g., Fat 75 g., Cal. 2000.

Food allowed in unlimited quantities :

Vegetables except potato.
Fruit, 3 or more helpings daily.
Soups made without fat.
Tea and coffee, milk and sugar from allowance.
Parsley, tomato juice, lemon, lemon juice, vinegar, herbs and spices.

Food allowed in limited quantities :

8 thin slices of bread, white or brown, *or* exchange (see below)..
½ pint milk.
3 helpings of lean meat *or* exchange.
6 teaspoonfuls jam, marmalade or honey.
1 oz. sugar, 5 teaspoonfuls.
2 potatoes, size of hen's eggs, *or* 2 tablespoonfuls of mashed potato, no added fat.
1 oz. oil (2 tablespoonfuls), to be used for salad dressing and for frying ; if used for frying put double the quantity into pan since some will remain unconsumed after cooking. Do not heat oil more than twice.

Foods to be avoided :

Fats including butter, margarine, lard, dripping, cooking fat, and fat of meat, bacon and ham.
Fatty meat, *e.g.* pork, goose, duck, tongue, and all tinned meat and sausages.
Cream, ice-cream. Cakes and pastry unless made with fat from allowance.
Chocolate, sweets. Chocolate, cream and fancy biscuits.
Sauces, mayonnaise or salad cream, unless made from foods allowed.
Puddings unless made from foods allowed.

Exchanges for helping of meat or 2 eggs :

Helping of hare, rabbit, liver, tripe, kidney, lean ham, veal, venison or any kind of poultry except goose or duck.
4 rashers of lean bacon, grilled, drained of fat and all visible fat removed.
Helping of any kind of fish.
1½ oz. of any kind of cheese except cream cheese.
One dozen oysters.

Exchanges for 1 slice bread :

3 water biscuits or 2 Ryvita or similar crispbread or 2 'Rich Tea' or similar type of plain biscuit or 2 oatcakes or 1 teacup of breakfast cereal or 3 tablespoonfuls of cooked porridge or ¾ oz. flour (level tablespoonful) or ⅔ oz. cereal, *e.g.* rice, semolina, tapioca, sago, cornflour, farola, custard powder.

SUGGESTIONS FOR USING VEGETABLE OIL

Frying :

Oil is suitable for all types of frying.

Grilling :

Food may be brushed with oil before grilling. This improves appearance and texture.

Stewing :

Oil may be used instead of dripping for stews and curry.

Sauces :

½ oz. flour.
½ oz. (1 tablespoonful) oil.
¼ to ½ pint liquid, may be water, vegetable water or milk from allowance.

Heat oil. Add flour and cook for 1 to 2 minutes. Gradually add liquid, stirring all the time. Cook for 5 minutes. Flavourings such as parsley, herbs, onion, tomato juice, curry powder, meat or vegetable extract may be added.

Scrambled egg :

1 egg.
Seasoning.
½ oz. (1 tablespoonful) oil.
1 to 2 tablespoonfuls milk from allowance.

Heat oil and milk. Add beaten egg and seasoning. Cook over gentle heat until set.

Porridge :

½ pint water.
Salt.
½ oz. (1 tablespoonful) oil.
1 heaped teaspoonful oatmeal.

Boil water, sprinkle in oatmeal, when boiling add oil and simmer until cooked.

Sautéed vegetables :

Heat oil, add chopped raw vegetables, season and allow to simmer until cooked.

Skirlie :

1 onion.
2 handfuls oatmeal.
1 oz. (2 tablespoonfuls) oil.
Seasoning.

Fry onion in oil till soft but not brown. Add oatmeal and seasoning and cook over low heat for 10 to 15 minutes till golden brown. May be served with meat or with potatoes and vegetables.

Sweets, sponge cake :

2 oz. sugar.
2 oz. flour.
1 egg.
2 oz. (4 tablespoonfuls) oil.
1 teaspoonful baking powder.
¼ teaspoonful salt.

Beat egg and oil. Add flour, sugar and baking powder. Mix to soft consistency with warm water. Bake in moderate oven till firm and golden brown.

Flavourings such as lemon, orange, spices, coffee, vanilla or coconut may be used.

Genoese sponge :

1 egg.
1 oz. flour.
1 oz. (2 tablespoonfuls) oil.
1⅓ oz. castor sugar.

Whisk egg and sugar over hot water till thick and creamy. Cool and add oil gradually. Fold in flour. Bake in hot oven 10 to 15 minutes.

Ginger nuts :

2 tablespoonfuls syrup.
4 oz. plain flour.
¼ teaspoonful salt.
½ teaspoonful mixed spices.
2 oz. (4 tablespoonfuls) oil.
2 teaspoonfuls baking powder.
½ teaspoonful ground ginger.
½ teaspoonful bicarbonate of soda.

Melt oil and syrup. Add to dry ingredients. Drop in spoonfuls on baking tray and bake in moderate oven till brown.

Fruit sauce :

½ oz. cornflour.
½ pint fruit juice.
½ oz. (1 tablespoonful) oil.

Make as for savoury sauce. Sweeten to taste. Sieved fruit may be added to make fool.

Fruit condé :

Cook rice in fruit juice. Sweeten to taste. Add a little milk from allowance and bake in oven till creamy. Allow to cool. Place sliced fruit on top and cover with fruit sauce (see above).

Brandy wafers :

2 oz. syrup.
2 oz. flour.
1¾ oz. castor sugar.
½ teaspoonful lemon juice.
1 oz. (2 tablespoonfuls) oil.
½ teaspoonful ground ginger.
½ teaspoonful grated lemon rind.

Melt syrup, sugar and oil in saucepan. Add dry ingredients. Drop in teaspoonfuls, well apart, on oiled baking tray. Bake in cool oven 7 to 10 minutes. When brown and set remove from tray and roll round handle of wooden spoon. Slip off carefully.

Gingerbread :

12 oz. flour.
2 oz. brown sugar.
¼ pint of milk.
½ teaspoonful bicarbonate of soda.
4 oz. (8 tablespoonfuls) oil.
2 teaspoonfuls ground ginger.
½ lb. syrup.

Mix ground ginger and sugar. Heat oil, syrup and milk. Mix into flour and other dry ingredients. Knead well. Dissolve bicarbonate of soda in 1 tablespoonful milk and add to mixture. Bake in slow oven 1 to 1¼ hours. (Use 8 in. square tin.)

DIET No. 13

LOW CALORIC DIET

with restricted salt regime suitable for patients with

SEVERE CARDIAC FAILURE

Approximately : Cal. 900, Sodium content 1 g.

Breakfast	1 thin slice of very crisp toast. Butter and milk from allowance.* Weak freshly made tea.
Mid-morning	Small glass of fruit juice.
Dinner	Small helping of white fish, chicken, sweetbreads *or* rabbit. 1 tablespoonful of sieved vegetable. Small helping of milk pudding made with milk from allowance.
Tea	1 thin slice of very crisp toast. Butter and milk from allowance. Weak freshly made tea.
Supper	Egg custard made with milk from allowance. Small helping of sieved fruit.
Bedtime	Milk drink made with remainder of milk from allowance.

* *Allowance for day :* ¾ pint (450 ml.) of milk.
½ oz. (15 g.) of butter.

No salt to be used in cooking or at table.

DIET No. 14

LOW SODIUM DIET

suitable for patients with

Membranous Glomerulonephritis
Congestive Heart Failure
The Nephrotic Syndrome with Marked Œdema [1]
Cirrhosis of the Liver with Ascites and Œdema [1]

Approximately : Sodium 0·5 g., Protein 60 g., Carbohydrate 250 g., Fat 60 g., Cal. 1800.

Breakfast	Fruit *or* fruit juice, sweetened as desired. 1 egg *or* small helping of white fish. 1½ thin slices of ' salt-free ' bread,[2] which may be toasted. Marmalade or honey. ' Salt-free ' butter and milk from allowance.* Tea or coffee, with sugar if desired.
Mid-morning	Tea or coffee with milk from allowance, *or* fruit *or* fruit juice.
Dinner	No soup. Small helping of tender meat, chicken, tripe, liver, sweetbread *or* white fish. Helping of sieved vegetables. Helping of mashed or creamed potato. Fruit—fresh, stewed or tinned—*or* jelly *or* whip made with egg white.
Tea	1½ thin slices of ' salt-free ' bread, which may be made into sandwiches using tomato, apple, banana, jam, jelly or honey. Home-made biscuit to which no bicarbonate of soda, salt, baking powder or salt butter has been added. ' Salt-free ' butter and milk from allowance. Tea with sugar if desired.
Supper	1 egg *or* small helping of meat *or* fish as at dinner. Fruit—fresh, stewed or tinned. 1½ thin slices of ' salt-free ' bread. Jam, jelly or honey. ' Salt-free ' butter and milk from allowance. Tea or coffee with sugar, if desired.

* *Allowance for day :* ½ pint (0·25 *l.*) of milk.
1 oz. (30 g.) ' salt-free ' butter or margarine.

Management :

No salt to be used in cooking or at table.

Avoid all cured meat and fish, *e.g.* bacon, ham, tongue, pickled brisket and silverside, finnan haddock, kippers, sardines, pilchards, smoked salmon ; all tinned foods except fruit ; bottled sauces, pickles, sausages and all foods made with bicarbonate of soda or baking powder.

To increase the calories the following may be added : sugar, fruit, jam, marmalade and boiled sweets and pastilles.

The specified amounts of ' salt-free ' bread and butter must not be exceeded, as they still contain appreciable amounts of sodium.

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[1] In nephrosis and cirrhosis a high protein intake is usually required : this is most easily obtained by adding a preparation of milk proteins (*e.g.* Casilan—Glaxo, or Lonalac—Mead Johnson), which is practically free of sodium (see text).

[2] See recipe on page 841.

RECIPE FOR 'SALT-FREE' BREAD

1¾ lb. of flour.	½ teaspoonful of castor sugar.
½ oz. yeast.	¾ pint of tepid water.

METHOD.—Sieve the flour into a large warm bowl. Cream the yeast and sugar together with a wooden spoon until liquid, and add the tepid water. Make a well in the centre of the flour, and strain in the yeast and water. Sprinkle a little of the flour over, cover the basin with a cloth, and set to rise in a warm place for 20 minutes till the surface is covered with bubbles. This is called 'setting the sponge.' Work in all the flour with the hand, adding more tepid water if necessary to make a firm, elastic dough, and knead thoroughly. Cover again with a cloth, and set to rise in a warm place for 2 hours. When well risen, knead the dough lightly on a floured board, and form into loaves. The dough may be put into warm greased tins. Place loaves in a warm place to prove for 15 minutes; then bake in a hot oven for 30 minutes to 1 hour, according to size of loaf. When ready, the bread will be well risen, will feel light, and when tapped underneath will sound hollow. If in a tin, turn out and place loaf on tray in oven in order to brown the sides. Then cool rapidly on a wire tray.

DIET No. 15

A sample menu for

MINIMAL SODIUM (RICE-FRUIT) DIET

suitable for patients with

SEVERE MALIGNANT HYPERTENSION NOT RESPONDING TO OTHER TREATMENT

Sodium content : below 0·2 g.

Breakfast	Grapefruit (prepared), 5 oz. (150 g.). Boiled rice (dry weight), 2 oz. (60 g.). Sugar, 1 oz. (30 g.). Orange juice, 8 oz. (250 ml.).
Mid-morning	Lemon juice, 1¼ oz. (37 g.), with water, 5 oz. (150 ml.). Sugar, ½ oz. (15 g.).
Dinner	Boiled rice (dry weight), 3 oz. (90 g.). Sugar, ½ oz. (15 g.). Blackcurrants, raw, 5 oz. (150 g.). Added sugar, 1 oz. (30 g.). Black grapes, 6 oz. (180 g.).
Tea	Boiled rice (dry weight), 1 oz. (30 g.). Sugar, 1 oz. (30 g.), for rice and fruit drink. Banana slices, 1½ oz. (45 g.), added to rice. Fruit drink made of : Orange juice, 2 oz. (60 ml.). Lemon juice, ½ oz. (15 ml.).
Supper	Boiled rice (dry weight), 3 oz. (90 g.). Sugar, ¾ oz. (22 g.). Fresh peaches, 5 oz. (150 g.). Orange juice, 8 oz. (240 ml.).
Before retiring	Dessert cherries, 5 oz. (150 g.).

DIET No. 16

LOW PROTEIN DIET

suitable for patients with

ACUTE NEPHRITIS OR
CHRONIC RENAL DISEASE WITH MARKED NITROGEN RETENTION

Approximately : Protein 45 g., Carbohydrate 245 g., Fat 60 g., Cal. 1700.

Breakfast	Fruit (fresh or stewed or tinned), *or* small glass of fruit juice. 1½ thin slices of bread, which may be toasted. Marmalade or honey. Butter and milk from allowance.* Tea with sugar.
Mid-morning	Tea or coffee with milk from allowance and sugar. 1 biscuit.
Dinner	Small helping of meat or poultry or fish, *or* 2 eggs scrambled or baked. Small helping of vegetables. 1 medium-size potato. Milk pudding, using milk from allowance and sugar. Fruit (fresh, stewed or tinned).
Tea	2 thin slices of bread with jam, jelly or honey, *or* may be made into sandwiches, using tomato, lettuce, cucumber, dates or banana. Butter and milk from allowance.
Supper	1 thin slice of bread or 2 biscuits. Jam, jelly or honey. Fruit (fresh, stewed or tinned). Butter and milk from allowance. Tea or coffee with milk from allowance and sugar.

* *Allowance for day :* ¾ pint (425 ml.) of milk.
1¼ oz. (37 g.) butter or margarine.

For patients with acute nephritis some restriction of fluid is necessary. No more than one cup of tea should be allowed on each occasion. Salt should not be used in cooking, nor should table salt be allowed.

For patients with chronic nephritis no restriction of the fluid or salt intake is usually necessary (Chapter 41).

DIET No. 17

HIGH PROTEIN DIET

suitable for patients with

The Nephrotic Syndrome including Membranous Glomerulonephritis

Approximately: Protein 100 g., Carbohydrate 250 g., Fat 120 g., Cal. 2500.

Breakfast	Fruit (fresh or stewed or tinned), *or* small glass of fruit juice. 2 eggs (poached, boiled or scrambled), *or* helping of white fish. 2 slices of bread, which may be toasted. Marmalade or honey. Butter and milk from allowance.* 1 cup of tea or coffee with milk and sugar from allowance.
Mid-morning	1 cup of tea or coffee with milk and sugar from allowance. 2 plain biscuits.
Dinner	Large helping of any kind of fresh meat, poultry, game or fish. Helping of vegetables. Helping of potato. Milk pudding, using milk from allowance. Fruit (fresh, stewed or tinned).
Tea	2 slices of bread, made into sandwiches, using egg, minced meat or chicken. Butter and milk from allowance. 1 cup of tea with milk and sugar from allowance.
Supper	Helping meat or fish, *or* 2 eggs poached, boiled, scrambled or as omelette, or baked egg or fish custard. Vegetables if desired. Milk pudding with milk from allowance and fruit (fresh or stewed), *or* 2 thin slices of bread with butter from allowance. Jam, jelly or honey. 1 cup of tea or coffee with milk and sugar from allowance.

* ***Allowance for day:*** 1 pint ($\frac{1}{2}$ *l.*) of milk.
1½ oz. (45 g.) butter or margarine.
2 oz. (60 g.) sugar.

The intake of salt must be restricted by not adding salt at table, by using minimal amounts in cooking and by avoiding salt-rich foods (p. 144).

DIET No. 18

RESTRICTED PROTEIN DIET

suitable for patients with

CHRONIC RENAL FAILURE OF MODERATE SEVERITY

Approximately : Protein 60 g., Carbohydrate 280 g., Fat 100 g., Cal. 2300.

Breakfast	Cornflakes or similar cereal with fruit or milk from allowance.* 1 egg, poached, boiled or scrambled, *or* 2 rashers of bacon or small helping of fish. 1½ thin slices of bread, which may be toasted. Marmalade or honey. Butter and milk from allowance. Tea or coffee with milk from allowance and sugar.
Mid-morning	Tea or coffee with milk from allowance and sugar, *or* fruit juice with glucose. 1 plain biscuit.
Dinner	Small helping any kind of meat, poultry, game or fish. Helping of vegetables. Helping of potato. Milk pudding with milk from allowance. Fruit (fresh, stewed or tinned).
Tea	2 thin slices of bread which may be made into sandwiches, using tomato, cucumber, lettuce, dates or banana, jam, jelly or honey. Butter and milk from allowance. Tea.
Supper	1 egg, poached, boiled, scrambled or as omelette with filling of tomato, asparagus or spinach, or baked egg with tomato or asparagus, *or* small helping of macaroni cheese, *or* fish kedgeree or fish cake. Vegetables if desired. Milk pudding with milk from allowance, *or* fruit (fresh, stewed or tinned). 1½ thin slices of bread. Jam, jelly or honey. Butter and milk from allowance. Tea or coffee.

* *Allowance for day :* ¾ pint (425 ml.) of milk.
2 oz. (60 g.) butter or margarine.

DIET No. 19

REFERENCE DIET

suitable for

ADULT DIABETICS

Approximately : Protein 100 g., Carbohydrate 180 g., Fat 100 g., Cal. 2000.

Breakfast	1 protein exchange. 3 carbohydrate exchanges. Butter and milk from allowance.* Tea or coffee (no sugar).
Mid-morning	1 carbohydrate exchange. Butter and milk from allowance. Tea or coffee (no sugar).
Dinner	Clear soup, if desired. 2 protein exchanges. 2 carbohydrate exchanges (1 to be taken as fruit). Vegetables from Group 2. Butter and milk from allowance.
Tea	1 protein exchange. 2 carbohydrate exchanges. Butter and milk from allowance. Tea (no sugar).
Supper	2 protein exchanges. 2 carbohydrate exchanges. Vegetables from Group 2. Butter and milk from allowance. Tea or coffee (no sugar).

* *Allowance for day :* 1 pint (0·5 *l.*) whole milk.
1½ oz. (45 g.) butter *or* 3 fat exchanges.

Part of the milk can be exchanged on the basis that 1 pint of milk is equivalent to 2 protein, 2 carbohydrate and 1 fat exchanges.

Avoid (unless expressly permitted) : sugar, glucose, sweets, honey, jam, jelly, marmalade, preserves, syrup, molasses, pastry, cake, cookies, sweet condensed milk, soft drinks, alcoholic drinks.

NOTE.—In this diet nearly half the calories are derived from fat. In middle-aged patients, especially if the plasma cholesterol is high or there is any evidence of ischæmic heart disease, one or more fat exchanges should be replaced by either carbohydrate or protein exchanges.

Dietary exchanges for diabetics

	Amount		Remarks
	oz.	g.	

1. CARBOHYDRATE EXCHANGES

Each exchange contains approximately 15 g. of carbohydrate, 3 g. of protein and 1 g. of fat. Caloric value is about 80

	oz.	g.	Remarks
Cereals—			
Bread	1	30	
Toast	¾	22	
Rice, oatmeal, wheatflour, cornflour, arrowroot, sago, tapioca, breakfast cereals	⅔	20	All in dry state
Rice, macaroni, spaghetti	2	60	Boiled
Porridge	6	180	Cooked
Biscuits and scones—			
Water, cream cracker, rich tea or digestive biscuits, crispbreads	⅔	20	
Oatcakes	1	30	
Scones and baps	¾	22	
Sponge cake, gingerbread	⅔	20	No icing or filling
Miscellaneous—			
Marmalade, jam	⅔	20	
White sauce (savoury)	5	150	
Soup (creamed, tinned or packet)	15	450	Prepared
Fruit—			
Brambles (blackberries), blackcurrants, redcurrants, raspberries	10	300	Raw or stewed
Grapefruit, melon, strawberries	10	300	Raw
Apricots, apples, cherries, gooseberries, pears, plums	10	300	Stewed
Apples, cherries, gooseberries, oranges, pears, pineapple, plums, peaches	5	150	Raw
Bananas	3	90	Without skin
Grapes	3	90	
Prunes	3	90	Stewed without sugar
Apricots, currants, dates, figs, peaches, prunes, raisins, sultanas	1	30	All in dry state
Vegetables (*Group* 1)—			
Dried peas, beans and lentils	1	30	
Potatoes—chip or roast	1½	45	
Potatoes boiled, tinned peas, baked beans, sweet corn	2½	75	
Parsnip, beetroot, fresh or frozen peas	5	150	Fresh and boiled

Vegetables (*Group* 2)—unrestricted—

The following vegetables can be eaten in unrestricted amounts: artichokes, asparagus, french beans, runner beans, brussels sprouts, cabbage, cauliflower, celery, cucumber, lettuce, marrow, mustard and cress, radish, spinach, tomatoes, turnips, watercress, carrots, leeks, onions, mushrooms, rhubarb.

2. PROTEIN EXCHANGES

Each exchange contains almost no carbohydrate, and approximately 8 g. of protein and 5 g. of fat. Caloric value is about 80

	oz.	g.	Remarks
Lean beef, mutton, pork, bacon, ham, poultry, game or offal	1	30	Cooked weight
Corned beef, tinned meats	1	30	
Meat paste, pâte	1½	45	
Egg (1)	2	60	
Cheese	1	30	
Fish (white, smoked or tinned), shellfish	1½	45	Cooked weight
Peas, beans, lentils (include 1 carbohydrate exchange)	1	30	In dry state
Sausage (includes ½ carbohydrate exchange)	2	60	Cooked

3. FAT EXCHANGES

Each exchange contains approximately 12 g. of fat and almost no carbohydrate or protein. Caloric value is about 110

	oz.	g.	Remarks
Butter, margarine, lard, dripping, cooking fat, olive oil or vegetable oil	½	15	
Cream—'single'	1	30	
Cream—'double'	¾	22	
Salad cream, mayonnaise	¾	22	
Nuts	¾	22	Shelled

DIET No. 20

A sample of

A MENU RESTRICTED IN CARBOHYDRATE

(Adapted from the Reference Diet No. 19)

suitable for patients with

DIABETES MELLITUS IN GREAT BRITAIN

Approximately : Protein 100 g., Carbohydrate 180 g., Fat 100 g., Cal. 2000.

Breakfast	Porridge (6 oz.) with milk from allowance. 1 egg. Bread (2 oz.) with butter from allowance.* Tea or coffee with milk from allowance.
Mid-morning	Biscuits (⅔ oz.). Tea or coffee with milk from allowance.
Dinner	Clear soup with shredded vegetables. Lean meat (2 oz.). Boiled potatoes (2½ oz.). Generous helping of vegetables (Group 2) either cooked or as salad. Orange (5 oz.). Milk from allowance taken with coffee or as curds.
Tea	Sandwiches containing meat, egg or cheese (1 protein exchange), using 2 oz. bread and butter from allowance. Tea with milk from allowance.
Supper	Lean meat (2 oz.). Tomato or other Group 2 vegetables. Bread (2 oz.). Tea or coffee with milk from allowance.

* *Allowance for day :* 1 pint milk (0·5 *l.*).
1½ oz. (45 g.) butter or margarine.

DIET No. 21

A MENU RESTRICTED IN CARBOHYDRATE

(Adapted from the Reference Diet No. 19)

suitable for

PATIENTS WITH DIABETES WHO ARE VEGETARIANS AND RICE-EATERS

Approximately : Protein 80 g., Carbohydrate 200 g., Fat 100 g., Cal. 2000.

		Protein	Carbo-hydrate	Fat
		g.	g.	g.
Morning	*Pongal* (rice 60 g. plus green gram 15 g.), ghee from allowance	7	52	...
	Ulundu vadai (black gram 30 g.), oil from allowance *	7	17	...
	Coffee using milk from allowance (without sugar).			
Mid-day	Rice (60 g.)	4	44	...
	Sambhar (15 g. red gram)	3	8	...
	Pappads (15 g.)	5	15	...
	Leafy green vegetables as required.†			
	Country vegetables as required.†			
	Curds (90 g.)	2	3	2
Evening	Sundal (field bean—' mochai ') (45 g.)	17	10	7
	Ground nuts, roasted (30 g.)	9	6	11
	Coffee, using milk from allowance (without sugar).			
Bedtime	*Chappatis* or *puris* (30 g. of wheat flour)	3	20	...
	Country vegetables as required.			
	Milk from allowance.			
* *Allowance for day :*	0·5 *l.* buffalo milk	24	28	45
	40 g. ghee and oil for cooking	...	...	36

Vegetables :

Group 1.—Any containing more than 3 per cent. of starch to be avoided unless introduced as a carbohydrate exchange—*e.g.* potatoes, colocacia, yam, sweet potato, tapioca, plantain fruit (ripe and unripe).

† *Group* 2.—Can be taken in unrestricted amounts : (*a*) leafy green vegetables—*e.g.* amaranth, cabbage, spinach ; (*b*) country vegetables—*e.g.* radish (white), ash gourd, bitter gourd (large), brinjal, broad beans, calabash cucumber, french beans, cluster beans, kovai, knol-knol, lady's finger, plantain flower, ridge gourd, snake gourd, tomato green, jack tender.

This menu was designed for us by Dr M. Krishnaswamy. It is based on South Indian foods and dietary customs, but could easily be modified for patients in other countries with the aid of a suitable list of exchanges comparable with those on page 847.

DIET No. 22

REFERENCE DIET

suitable for

A DIABETIC CHILD AGED 4 TO 6 YEARS

Approximately : Protein 70 g., Carbohydrate 165 g., Fat 80 g., Cal. 1650.

Breakfast	1 protein exchange.[*] 2 carbohydrate exchanges. Butter and milk from allowance.[†] Tea if desired.
Mid-morning	1 carbohydrate exchange. Milk from allowance.
Dinner	1 protein exchange. 2 carbohydrate exchanges (1 to be taken as fruit). Vegetables from Group 2 (p. 847). Butter and milk from allowance.
Tea	1 protein exchange. 2 carbohydrate exchanges. Vegetables from Group 2 as desired. Butter and milk from allowance. Tea if desired.
Supper	2 carbohydrate exchanges. Butter and milk from allowance.

[*] For exchanges see page 847.

[†] *Allowance for day :* 1 pint (0·5 *l.*) milk.
1 oz. (30 g.) butter *or* 2 fat exchanges.

DIET NO. 23

A GOOD WELL-BALANCED DIET

suitable for

CONVALESCENT PATIENTS (MEDICAL OR SURGICAL)

Approximately : Cal. 3000 to 3300.

Early morning	Fruit juice with sugar *or* cup of tea with piece of toast.
Breakfast	Fruit *or* fruit juice. Porridge *or* breakfast cereal. Bacon and egg *or* egg, poached, boiled, scrambled or as omelette, *or* cold ham, fish, sausage or kidney. Bread or toast. Butter and marmalade or honey. Tea or coffee with milk and sugar as desired.
Mid-morning	Tea, coffee, milk or milk drink. Biscuits.
Dinner	Soup *or* grapefruit, melon, fruit or tomato juice, *or* pâté. Helping of any kind of meat, poultry, game or fish. Helping of vegetables. Helping of potato. Milk pudding with fruit *or* light steamed pudding *or* soufflé, whip, mousse, tart or pie *or* egg custard with fruit, pancakes or sweet omelette. Biscuits with cheese. Tea or coffee if desired.
Tea	Sandwiches with filling of egg, cheese, meat, sardines, dates, banana, apple, lettuce, tomato, cucumber, meat or yeast extract, honey, or jam. Cake or biscuit. Tea with milk and sugar as desired.
Supper	Egg or cheese dish *or* any kind of meat or fish as at dinner. Vegetable if desired. Bread, toast and/or scone with butter, jam, honey or cheese. *or* Sweet as at dinner. Biscuits and cheese. Tea or coffee with milk and sugar as desired.
Bedtime	Milk drink. Biscuits.
Allowance for day :	1½ to 2 pints (0·75 to 1 *l.*) of milk. 2 to 2½ oz. (60 to 75 g.) butter and cooking fat. Cream can be used as desired. Butter or margarine should be added to food where possible, *e.g.* to vegetables and potatoes. Sweets and chocolate may be taken after meals. Beer, stout or wine may be taken with meals.

TABLE OF WEIGHTS AND MEASURES

WEIGHTS

		Approximate equivalents used in this book.
1 ounce (oz.)	=28·35 g.	30 g.
1 pound (lb.)	=453·6 g.	
1 stone	=6·35 kg.	
1 gram (g.)	=0·0353 oz.	
1 kilogram (kg.)	=2·205 lb.	2·2 lb.

FLUID MEASURES

1 fluid ounce (fl. oz.)	=28·41 ml.	30 ml.
1 pint	=568·2 ml.	500 ml.
1 (English) gallon	=4·546 *l.*	
	=1·2 U.S.A. gallons	
1 teaspoonful	=$\frac{1}{8}$ fl. oz.	4 ml.
1 dessertspoonful	=$\frac{1}{4}$ fl. oz.	8 ml.
1 tablespoonful	=$\frac{1}{2}$ fl. oz.	15 ml.
1 millilitre (ml.)	=0·0352 fl. oz.	
1 litre (*l.*)	=1·760 pints	

MEASURES OF LENGTH

1 inch (in.)	=2·54 cm.	
1 foot	=30·48 cm.	30 cm.
1 mile	=1·609 km.	
1 centimetre (cm.)	=0·394 in.	
1 kilometre (km.)	=0·6214 mile	

REFERENCES

Abrahams, A. (1956). *The Human Machine.* Harmondsworth, Middlesex: Penguin Books.

Adams, C. W. M. (1959). *Lancet,* **1,** 1075.

Adcock, L. H. & Gray, C. H. (1957). *Biochem. J.* **65,** 554.

Addis, T., Poo, L. J. & Lew, W. (1936). *J. biol. Chem.* **116,** 343.

Adlersberg, D. & Schaefer, L. E. (1959). *Amer. J. Med.* **26,** 1.

Adlersberg, D., Schaefer, L. E. & Steinbert, A. G. (1956). *J. Amer. med. Ass.* **162,** 619.

Agate, J. N. & 12 others (1949). *Medical Research Council,* Memo. No. 22.

Ahlman, K. L., Eränko, C., Karvonen, M. J. & Lepänen, V. (1952). *J. appl. Physiol.* **4,** 911.

Ahrens, E. H. and 5 others (1957). *Lancet,* **1,** 943.

Ahrens, E. H. and 7 others (1959). *Lancet,* **1,** 115.

Albright, F. & Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease.* Baltimore: Williams & Wilkins.

Albrink, M. J. & Man, E. V. (1959). *Arch. int. Med.* **103,** 4.

Alrdrich, C. A. & Boyle, H. H. (1933). *J. Amer. med. Ass.* **100,** 1979.

Alison, A. C. & Clyde, D. F. (1961). *Brit. med. J.* **1,** 1346.

Allison, J. B. (1955). *Physiol. Rev.* **35.** 664.

Al-Witry, H., Shaby, J. A. & Kantarjian, A. D. (1950). *J. Fac. Med. Iraq,* **14,** 143.

Amarjit Sing, Jolly, S. S. & Kumar, L. R. (1961). *Lancet,* **1,** 587.

Anand, B. K. (1961). *Physiol. Rev.* **41, 677.**

Anand, B. K., Dua, S. & Schoenbert, K. (1955). *J. Physiol.* **127,** 143.

Anderson, C. M. and 5 others (1952). *Lancet,* **1,** 836.

Andrews, R. H. and 5 others (1960). *Bull. Wld Hlth Org.* **23,** 436; **24,** 129, 149.

Andross, M. (1946). *Proc. Nutr. Soc.* **4,** 155.

Anonymous (1953). *Lancet,* **2,** 447.

Archer, H. E., Dormer, A. E., Scowen, E. F. & Watt, R. W. E. (1957). *Lancet,* **2,** 320.

Arneil, G. C. (1961). *Lancet,* **2,** 1103.

Aschoff, L. & Koch, W. (1919). *Scorbut: eine Pathologisch-Anatomische Studie.* Jena: Fischer.

Ashley, B. C. E. & Whyte, H. M. (1961). *Aust. Ann. Med.* **10,** 92.

Astrup, T. (1956). *Lancet,* **2,** 565.

Astwood, E. B. (1943). *J. Pharmacol.* **78,** 79.

Atwater, W. O. & Benedict, F. G. (1899). *Experiments on the Metabolism of Matter and Energy in the Human Body.* Bulletin No. 69, p. 76. Washington: U.S. Department of Agriculture.

—— —— (1902). *Mem. Nat. Acad. Sci. Wash.* **8,** 231.

Auden, G. A. (1923). *J. roy. sanit. Inst.* **44,** 236.

Aykroyd, W. R. (1930). *J. Hyg. (Camb.),* **30,** 357.

—— (1951). Revised by Patwardhan, V. N. & Ranganathan, S. *Indian Res. Fund. Ass. Hlth Bull.* No. 23.

—— (1957). *Ann. Nutr. Paris,* **11,** 171.

Aykroyd, W. R. & Swaminathan, M. (1940). *Indian J. med. Res.* **27,** 667.

Aykroyd, W. R., Madhava, K. B. & Rajagopal, K. (1938). *Indian J. med. Res.* **26,** 55.

Aykroyd, W. R., Krishnan, B. G., Passmore, R. & Sundararajan, A. R. (1940). *Indian med. Res. Mem.* No. 32.

Badenoch, J. & Fourman, P. (1954). *Quart. J. Med.* **23,** 165.

Baird, D. (1960). *Lancet,* **2,** 557.

Balasubrahmanyan, M. & Chopra, H. L. (1960). *Indian J. med. Sci.* **14,** 351.

Balch, H. H. (1950). *J. Immunol.* **64,** 397.

Barcroft, J. (1944). *Proc. Nutr. Soc.* **1,** 192.

Barer, A. P. & Fowler, W. M. (1936). *Amer. J. Obstet. Gynec.* **31,** 979.

Barger, G. (1931). *Ergot and Ergotism.* London: Gurney & Jackson.

Barnet, H. L. (1956). *Infant Metabolism.* World Health Organization Seminar, p. 4. New York: Macmillan.

Barnicot, N. A. (1951). *J. Anat. (Lond.),* **85,** 120.

Bartley, W., Krebs, H. A. & O'Brien, J. R. P. (1953). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 280.

Bastenie, P. A. (1947). *Lancet,* **2,** 289.

Basu, K. P. (1946). *Indian Res. Fund. Ass. spec. Rep.* No. **15.**

Basu, K. P. & Basak, M. N. (1939). *Indian J. med. Res.* **27,** 115.

Baumann, E. (1895). *Z. physiol. Chem.* **21,** 319.

Bean, W. B., Vilter, R. W. & Blankenhorn, M. A. (1949). *J. Amer. med. Ass.* **140,** 872.

Beaton, G. H. (1961). *Fed. Proc.* **20**, Suppl. 7, 196.

Behnke, A. R., Feen, B. G. & Welham, W. C. (1942). *J. Amer. med. Ass.* **118,** 495.

Benjamin, B. (1962). *J. roy. statist. Soc. A.* **125,** 378.

Bergström, S. & Borgström, B. (1955). In *Progress in the Chemistry of Fats and other Lipids*, vol. 3, ed. R. T. Holman, W. O. Lundberg & T. Malkin. London: Pergamon.

Berlin, R. (1948). *Acta med. scand.* **129,** 560.

Bertram, G. C. L. (1954). *Proc. Nutr. Soc.* **13,** 69.

Bessey, O. A. & Wolbach, S. B. (1939). *J. exp. Med.* **69,** 1.

Best, C. H. & Taylor, N. B. (1961). *The Physiological Basis of Medical Practice*, 7th ed., p. 850. London: Baillière.

Best, C. H., Lucas, C. C. & Ridout, J. H. (1956). *Brit. med. Bull.* **12,** 9.

Beveridge, J. M. R., Connell, W. F. & Mayer, G. A. (1956). *Canad. J. Biochem.* **34,** 441.

Bibile, S. W., Lionel, N. D. W., Dunuwille, R. & Perera, G. (1957). *Brit. J. Nutr.* **11,** 434.

Biörck, G., Blomqvist, G. & Sievers, J. (1957). *Acta med. scand.* **145,** 494.

Birch, T. W. & Gyorgyi, P. (1936). *Biochem. J.* **30,** 304.

Bjurulf, P. (1959). *Acta med. scand.* **66,** Suppl. 349.

Black. D. A. K. (1957). *Essentials of Fluid Balance.* Oxford: Blackwell.

Black, W. A. P. (1953). *Proc. Nutr. Soc.* **12,** 32.

Blagg, C. R., Parsons, F. M. & Young, C. A. (1962). *Lancet,* **1,** 608.

Block, R. J. & Mitchell, H. H. (1946). *Nutr. Abstr. Rev.* **16,** 249.

Bloom, W. L. (1959). *Metabolism,* **8,** 214.

Blumenthal, C. J. (1950). *S. Afr. med. J.* **24,** 191.

Bøe, J., Humerfelt, S. & Wedervang, F. (1957). *Acta med. scand.* Suppl. 321.

Bombard, A. (1953). *The Bombard Story.* London: Andre Deutsch.

Bonnett, R. and 5 others (1955). *Nature,* **176,** 328.

Borrow, A., Fowden, L., Stedman, M. M., Waterlow, J. C. & Webb, R. A. (1948). *Lancet,* **1,** 752.

Bötcher, C. J. F., Boelsma-van Houte, E., ter Haar Romeny Watcher, C. Ch., Woodford, F. P. & van Gent, C. M. (1960). *Lancet,* **2,** 1162.

Bothwell, T. H. & Bradlow, B. A. (1960). *Arch. Path.* **70,** 279.

Boussingault, J. B. (1831). *Ann. Chim. (Phys.),* **48,** 41.

Bragdon, J. H. (1959). *Ann. N.Y. Acad. Sci.* **72,** 845.

Bramwell, E. (1925). *Brit. med. J.* **2,** 470.

Bras, G. & Hill, K. R. (1956). *Lancet,* **2,** 161.

Bray, B. (1953). *Brit. J. Nutr.* **7,** 3.

Brimblecombe, F. S. W., Blainey, J. D., Stoneman, M. E. R. & Wood, B. S. B. (1961). *Brit. med. J.* **2,** 793.

Brinton, D. (1946). *Proc. R. Soc. Med.* **39,** 173.

Bristowe, W. S. (1953). *Proc. Nutr. Soc.* **12,** 44.

British Medical Association (1950). *Report of the Committee on Nutrition.* London: B.M.A.

British Medical Journal (1961). **1,** 1377.

British Nutrition Society (1957). *Proc. Nutr. Soc.* **16,** 37.

Brobeck, J. R. (1948). *Yale J. Biol. Med.* **20,** 545.

—— (1957). *Yale J. Biol. Med.* **29,** 565.

Brobeck, J. R., Larsson, S. & Reyes, E. (1956). *J. Physiol.* **132,** 358.

Brobeck, J. R., Teppermann, J. & Long, C. N. H. (1943). *Yale J. Biol. Med.* **15,** 831.

Brock, J. F. (1961). *Recent Advances in Human Nutrition*, p. 145. London: Churchill.

Brock, J. F. & Autret, M. (1952). *Kwashiorkor in Africa.* WHO Monograph Series No. **8.** Geneva: WHO.

Bronte-Stewart, B. (1953). *Quart. J. Med.* **22,** 309.

—— (1961). In *Recent Advances in Human Nutrition*, p. 195, ed. J. F. Brock. London: Churchill.

Bronte-Stewart, B., Keys, A. & Brock, J. F. (1955). *Lancet,* **2,** 1103.

Bronte-Stewart, B., Antonis, A., Eales, L. & Brock, J. F. (1956). *Lancet,* **2,** 521.

Brown, J. B. (1959). *Nutr. Rev.* **17,** 321.

Brown, W. R., Hansen, A. E., Burr, G. O. & McQuarrie, I. (1938). *J. Nutr.* **16,** 511.

Brozek, J. (1956). *Body Measurements and Human Nutrition.* Detroit: Wayne University Press.

Brozek, J. & Grande, F. (1955). *Hum. Biol.* **27,** 22.

Brozek, J. & Henschel, A. (1961). *Techniques for Measuring Body Composition.* Washington: National Academy of Sciences, National Research Council.

Bruce-Lockhart, Sir Robert (1960). *Scotch*, 2nd ed. London: Putnam.

Brunner, D. & Manelis, G. (1960). *Lancet,* **2,** 1049.

Burger, G. C. E., Drummond, J. C. & Sandstead, H. R. (1948). *Malnutrition and Starvation in Western Netherlands, September 1944 to July 1945.* The Hague : General State Printing Press.

Burnett, C. H., Commons, R. R., Albright, F. & Howard, J. E. (1949). *New Engl. J. Med.* **240,** 787.

Burr, G. O. & Burr, M. M. (1929). *J. biol. Chem.* **82,** 345.

Butson, A. R. C. (1950). *Lancet,* **1,** 993.

Butt, A. J. (1956). *Etiologic Factors in Renal Lithiasis.* Springfield, Ill. : Thomas.

Buzard, J., Bishop, C. & Talbott, J. H. (1952). *J. biol. Chem.* **196,** 179.

Calder, Ritchie (1952). *Men against the Desert.* London : Allen & Unwin.

Cartwright, G. E. (1955). *Amer. J. clin. Nutr.* **3,** 11.

Cartwright, G. E. & Wintrobe, M. M. (1955). In *Modern Trends in Blood Diseases,* pp. 183-211, ed. J. F. Wilkinson. London : Butterworth.

Castle, W. B. (1929). *Amer. J. med. sci.* **178,** 748.

—— (1955). *New Engl. J. Med.* **249,** 603.

Cathcart, E. P. & Cuthbertson, D. P. (1931). *J. Physiol.* **72,** 349.

Central and Scottish Health Services Councils (1957). *Report of the Joint Sub-Committee on Welfare Food.* London : H.M.S.O.

Chakravarty, A., Sur, A. M. & Kandelwal, M. K. (1958). *Indian J. Child Hlth,* **7,** 521.

Chalmers, T. M., Pawan, G. L. S. & Kekwick, A. (1960). *Lancet,* **2,** 6.

Chanda, N. K. (1958). *Brit. med. J.* **1,** 1263.

Chandra, H., Venkatachalam, P. S., Belavadi, B., Reddy, V. & Gopalan, C. (1960). *Indian J. Child Hlth,* **9,** 589.

Chantrenne, H. (1961). *The Biosynthesis of Proteins.* Oxford : Pergamon Press.

Chargaff, E. & Davidson, J. N. (1960). *The Nucleic Acids,* vols. 1-3. New York & London : Academic Press.

Charmot, G. (1954). *Méd. Trop.* **14,** 689.

Chatfield, Charlotte (1949). *Food Composition Tables for International Use.* Washington : FAO.

—— (1954). *Food Composition Tables for International Use—Minerals and Vitamins.* Rome : FAO.

Chesney, A. M., Clawson, T. A. & Webster, B. (1928). *Bull. Johns Hopk. Hosp.* **43,** 261.

Chick, H. (1951). *Nutr. Abstr. Rev.* **20,** 523.

Chick, H. & Slack, E. B. (1945). *Biochem. J.* **39,** 22.

—— —— (1946). *Lancet,* **2,** 601.

Chick, H. and 5 others (1923). *Spec. Rep. Ser. med. Res. Coun. Lond.* No. **77.**

Chick, H., Macrae, T. F., Martin, A. J. P. & Martin, C. J. (1938). *Biochem. J.* **32,** 12.

Chittenden, R. H. (1909). *The Nutrition of Man.* London : Heinemann.

Chowdury, S. R., Rapagopal, K. & Chakrabarty, A. N. (1954). *Indian med. Gaz.* **89,** 283.

Christensen, E. H. (1953). In *Ergonomics Society Symposium on Fatigue,* p. 93, ed. W. F. Floyd & A. T. Welford, London : Lewis.

Claudien, J. (1958). *Bull. sci. roum.* **IV-V,** 65.

Clarke, C. A. & Sircus, W. (1952). *Lancet,* **2,** 113.

Clements, F. W. (1955). *Med. J. Aust.* **2,** 369.

Cohen, A. M., Bavly, S. & Poznanski, R. (1961). *Lancet,* **2,** 1399.

Cohen, H. (1957). *Report of the Joint Sub-committee on Welfare Foods.* London : H.M.S.O.

College of General Practitioners Working Party (1962). *Brit. med. J.* **1,** 1497.

Combe, J. S. (1824). *Trans. med.-chir. Soc. Edinb.* **1,** 194.

Commonwealth Consultative Committee (1960). *The Colombo Plan for Co-operative Economic Development in South and South-East Asia.* Ninth Annual Report of the Committee. Cmd. **1251.** London : H.M.S.O.

Consolazio, C. F., Johnson, R. E. & Pecora, E. (1963). *Physiological Methods of Metabolic Functions.* New York : McGraw-Hill.

Cook, J. (1777). *A Voyage towards the South Pole and round the World,* vol. 2, p. 112. London : Printed for W. Strahan and T. Cadell.

Cook, J. W. & Loudon, J. D. (1952). In *The Alkaloids,* vol. 2, p. 261, ed. R. H. F. Manske & H. L. Holmes. New York : Academic Press.

Cook, J. W., Duffy, E. & Schoental, R. (1950). *Brit. J. Cancer,* **4,** 405.

Cook, R. P. (1942). *Nutr. Abstr. Rev.* **12,** 1.

—— (1958). *Cholesterol.* New York : Academic Press.

Cooke, A. M. (1955). *Lancet,* **1,** 877, 929.

Corry Mann, H. C. (1926). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 106.

Country Doctor (1960). *Facing Retirement.* London : Allen & Unwin.

Cowan, H. K. (1955). *Practitioner,* **174,** 645.

CRANDON, J. H., LUND, C. C. & DILL, D. B. (1940). *New Engl. J. Med.* **223,** 353.
CRANE, R. K. (1960). *Physiol. Rev.* **40,** 789.
CRAWFORD, M. A. (1962). *Lancet,* **1,** 352.
CRICK, F. H. C. & WATSON, J. D. (1954). *Proc. roy. Soc. A.* **223,** 80.
CRITCHLEY, M. (1943). *The Shipwreck Survivor—A Medical Study.* London: Churchill.
CROWLEY, L. V. and 7 others (1956). *Metabolism,* **5,** 245.
CRUICKSHANK, E. K. (1952). *Vitam. & Horm.* **10,** 1.
—— (1956). *W. Indian med. J.* **5,** 147.
CRUICKSHANK, E. K., MONTGOMERY, R. D. & SPILLANE, J. D. (1961). *World Neurology,* **2,** 199.
CRUICKSHANK, E. W. H., DUCKWORTH, J., KOSTERLITZ, H. W. & WARNOCK, G. M. (1945). *J. Physiol.* **104,** 41.
CUTHBERTSON, D. P. (1930). *Biochem. J.* **24,** 1245.
—— (1959). *Metabolism,* **8,** 787.
CUTHBERTSON, D. P. & MUNRO, H. N. (1939). *Biochem. J.* **33,** 128.

DAHLQVIST, A. & BORGSTRÖM, B. (1961). *Biochem. J.* **81,** 411.
DALYELL, E. J. & CHICK, H. (1921). *Lancet,* **2,** 842.
DAM, H. (1935). *Biochem. J.* **29,** 1273.
DAM, H. & SCHÖNHEYDER, F. (1934). *Biochem. J.* **28,** 1355.
DARBY, W. J. and 5 others (1960). *Publ. Hlth Rep. Wash.* **75,** 738.
DARROW, D. C. & PRATT, E. L. (1950). *J. Amer. med. Ass.* **143,** 365, 432.
DAVIDSON, J. N. (1960). *The Biochemistry of the Nucleic Acids,* 4th ed. London and New York: Methuen.
DAVIDSON, L. S. P. (1944). *Edinb. med. J.* **51,** 184.
DAVIDSON, L. S. P. & FULLERTON, H. W. (1938). *Edinb. med. J.* **45,** 1.
DAVIDSON, L. S. P. & GIRDWOOD, R. H. (1947). *Brit. med. J.* **1,** 587.
DAVIDSON, L. S. P. & GULLAND, G. L. (1930). *Pernicious Anæmia.* London: Kimpton.
DAVIDSON, L. S. P. & SMITH, J. (1936). *Quart. J. Med.* **29,** 263.
DAWBER, T. R., MOORE, F. E. & MANN, G. V. (1957). *Amer. J. publ. Hlth.* **47,** April suppl., p. 4.
DAWSON, D. W., LEEMING, J. T., OELBAUM, M. H., PENGELLY, C. D. S. & WILKINSON, J. F. (1961). *Lancet,* **2,** 10.
DEAN, R. F. A. (1953). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 279.
DEAN, R. F. A. & SCHWARTZ, R. (1953). *Brit. J. Nutr.* **7,** 131.
DE CASTRO, J. (1952). *Geography of Hunger.* London: Gollancz.
DE MAEYER, E. M. (1954). *Ann. Soc. belge Méd. trop.* **34,** 139.
DENNY-BROWN, D. (1947). *Medicine,* **26,** 41.
Department of Experimental Medicine, Cambridge (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. **275.**
DEUEL, H. J. (1957). *The Lipids,* vols. 1-3. London & New York: Interscience Publishers.
DE WARDENER, H. E. & LENNOX, B. (1947). *Lancet,* **1,** 11.
DICKE, W. K. (1950). *Thesis.* University of Utrecht.
DIGGORY, P. L. C. & TOMKINSON, J. S. (1962). *Lancet,* **2,** 370.
DOCK, W. (1940). *Trans. Ass. Amer. Phycns,* **55,** 61.
DODDS, E. C. (1950). *Proc. R. Soc. Med.,* **43,** 342.
—— (1953). *Lancet,* **1,** 1211.
DOGRA, J. R. (1940). *Indian J. med. Res.* **28,** 145, 481.
DOLE, V. P. (1958). In *Chemistry of Lipids in Relation to Atherosclerosis,* p. 189, ed. I. H. Page. Springfield, Illinois: Thomas.
DOLL, R. & HANINGTON, E. (1961). *Pathologie et Microbiologia,* **24,** 531.
DOLL, R. & HILL, A. B. (1954). *Brit. med. J.* **1,** 1451.
DONOVAN, D. (1848). *Dublin med. Press,* **19,** 67.
DOROLLE, P. (1953). *Chron. Wld Hlth Org.* **7,** 355.
DORRIS, R. J. & STUNKARD, A. J. (1957). *Amer. J. med. Sci.* **223,** 622.
DOW, D. J. & STEVEN, D. M. (1941). *J. Physiol.* **100,** 256.
DOWDLE, E. B., SCHACHTER, D. & SCHENKER, H. (1960). *Amer. J. Physiol.* **198,** 609.
DRUMMOND, J. C. (1939). *Chem. and Ind.* **57,** 808, 827, 914.
DRUMMOND, J. C. & WILBRAHAM, A. (1935). *Lancet,* **2,** 459.
—— —— (1939). *The Englishman's Food.* Revised D. Hollingsworth (1958). London: Cape.
DUCKWORTH, J. & WARNOCK, G. M. (1942). *Nutr. Abstr. Rev.* **12,** 167.
DUDLEY, H. A. F. (1958). *Principles of General Surgical Management.* Edinburgh: Livingstone.
—— (1961). In *Textbook of Medical Treatment,* 8th ed. p. 906, ed. Sir Derrick Dunlop, Sir Stanley Davidson & S. Alstead. Edinburgh: Livingstone.
DUGUID, J. B. (1954). *Lancet,* **1,** 891.

DUGUID, J. B. & ROBERTSON, W. B. (1957). *Lancet*, **1**, 1205.

DUNCAN, L. J. P., ROSE, K. & MEIKLEJOHN, A. P. (1960). *Lancet*, **1**, 1262.

DUNLOP, D. M., DAVIDSON, L. S. P. & ALSTEAD, S. (1961). *Textbook of Medical Treatment*, 8th ed., p. 323. Edinburgh : Livingstone.

DUNNINGAN, M. G. and 5 others (1962). *Scot. med. J.* **7**, 159.

DURNIN, J. V. G. A. (1961*a*). *J. Physiol.* **156**, 294.

—— (1961*b*). *Geront. clin.* (*Basel*), **4**, 128.

DURNIN, J. V. G. A., BLAKE, E. C. & BROCKWAY, J. M. (1957). *Brit. J. Nutr.* **11**, 85.

DURNIN, J. V. G. A., BLAKE, E. C., BROCKWAY, J. M. & DRURY, E. A. (1961*a*). *Brit. J. Nutr.* **15**, 499.

DURNIN, J. V. G. A. and 6 others (1961*b*). *Brit. J. Nutr.* **15**, 587.

EDHOLM, O. G., FLETCHER, J. G., WIDDOWSON, E. M. & MCCANCE, R. A. (1955). *Brit. J. Nutr.* **9**, 286.

EDWARDS, R. D. & WILLIAMS, T. D. (1956). *The Great Famine*, p. 274. Dublin : Brown & Nolan.

EIJKMAN, C. (1897). *Virchows Arch. path. Anat.* **149**, 187.

ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M. & WOOLEY, D. W. (1937). *J. Amer. chem. Soc.* **59**, 1767.

EMERSON, R. G. (1962). *Brit. med. J.* **2**, 516.

EVANS, H. M. & BISHOP, K. S. (1923). *J. Amer. med. Ass.* **81**, 889.

FARQUHAR, J. W., SHANNON, D. G. & BATCHELOR, A. D. R. (1961). *Lancet*, **2**, 537.

FARQUHAR, J. W., KANSAS, E. T. & TAIT, H. P. (1962). *Lancet*, **2**, 498.

FEARNLEY, G. R. (1961). *Lancet*, **1**, 992.

FEARNLEY, G. R., FERGUSON, J., CHAKRABARTI, R. & VINCENT, C. T. (1960). *Lancet*, **1**, 184.

FISHER, R. B. (1954). *Protein Metabolism*. London : Methuen.

FITZGERALD MOORE, D. G. (1937). *W. Afr. med. J.* **9**, 35.

FLEISCH, A. (1951). *Helv. med. Acta*, **18**, 23.

FLETCHER, R. F. & MCCRIRICK, M. Y. (1958). *Brit. med. J.* **2**, 299.

FLETCHER, W. (1907). *Lancet*, **1**, 1776.

FLOREY, H. W. (1955). *Proc. roy. Soc. B.* **143**, 147.

—— (1960). *Brit. med. J.* **2**, 1329.

FLOREY, H. W., WRIGHT, R. D. & JENNINGS, M.A. (1941). *Physiol. Rev.* **21**, 36.

Food and Agriculture Organisation (1948). *Nutrition Meeting Report Series*, No. 2. Washington : FAO.

—— (1949). *Synthetic Fats : Their Potential Contribution to World Food Requirements.* Nutrition Studies, No. 2. Washington : FAO.

—— (1953*a*). *Maize Diets.* Nutritional Studies, No. 9. Rome : FAO.

—— (1953*b*). *School Feeding.* Nutritional Studies, No. 10. Rome : FAO.

—— (1954*a*). *Rice and Rice Diets.* Nutritional Studies, No. 1. Rome : FAO.

—— (1954*b*). *Rice Enrichment in the Phillippines.* Nutritional Studies, No. 12. Rome : FAO.

—— (1956). Report of an International Seminar on Education in Public Health and Nutrition. *Nutrition Meetings Report Series*, No. 13. Rome : FAO.

—— (1957*a*). *Calorie Requirements.* Nutritional Studies, No. 15. Rome : FAO.

—— (1957*b*) *Protein Requirements.* Nutritional Studies, No. 16. Rome : FAO.

—— (1960). Symposium on Education and Training in Nutrition in Europe. *Nutrition Meetings Report Series*, No. 26. Rome : FAO.

—— (1962). Calcium Requirements. *Nutrition Meetings Report Series*, No. 30. Rome : FAO.

—— (1963). *World Food Program.* Rome : FAO.

Food and Agriculture Organization/World Health Organisation (1951). *Tech. Rep. Wld Hlth Org.* No. 45.

—— (1955). *Tech. Rep. Wld Hlth Org.* No. 97.

—— (1957). *Tech. Rep. Wld Hlth Org.* No. 129.

—— (1958*a*). *Tech. Rep. Wld Hlth Org.* No. 144.

—— (1958*b*). *Tech. Rep. Wld Hlth Org.* No. 149.

—— (1959). *Nutrition Seminar. Belgian Congo*, 1959. Rome : FAO.

—— (1960). *Tech. Rep. Wld Hlth Org.* No. 197.

—— 1961*a*). *Tech. Rep. Wld Hlth Org.* No. 220.

—— (1961*b*). *Tech. Rep. Wld Hlth Org.* No. 245.

—— (1962). *Tech. Rep. Wld Hlth Org.* No. 228.

Food and Nutrition Board, National Academy of Sciences (1953). *Recommended Dietary Allowances.* National Research Council Publication, 302. Washington.

FORFAR, J. O. & TOMPSETT, S. L. (1959). *Adv. clin. Chem.* **2**, 167.

FOX, W. (1962). *Lancet*, **2,** 413, 473.
FOY, H. & KONDI, A. (1957). *J. trop. Med. Hyg.* **60,** 105.
FRANKLIN, K. J. (1960). *Proc. Nutr. Soc.* **19,** 108.
FRANZ, R. C., KARK, A. E. & HATHORN, M. (1961). *Lancet*, **1,** 195.
FRANZEN, R. & PALMER, G. T. (1934) *The ACH Index of Nutritional Status.* New York : American Child Health Association.
FRAZER, A. C. (1946). *Physiol. Rev.* **26,** 103.
—— (1958). *Brit. med. Bull.* **14,** 212.
FRAZER, A. C., SCHULMAN, J. H. & STEWART, H. C. (1944). *J. Physiol.* **103,** 306.
FRIIS-HANSEN, B. J., HOLIDAY, M., STAPLETON, T. & WALLACE, W. M. (1951). *Pediatrics*, **7,** 321.
FRITZ, I. B. (1961). *Physiol. Rev.* **41,** 52.
FROST, D. V. (1960). *Nutr. Rev.* **18,** 129.
FUCHS, A. M. & STRAUSS, M. B. (1960). In *Modern Nutrition in Health and Disease*, 2nd ed., p. 812, ed. M. G. Wohl & R. S. Goodhart. London : Kimpton.
FULLERTON, H. W. (1936). *Brit. med. J.* **2,** 577.
—— (1955). *Proc. R. Soc. Med.* **48,** 664.
FULLERTON, H. W., DAVIE, W. J. A. & ANASTASOPOULOS, G. (1953). *Brit. med. J.* **2,** 250.
FUNK, C. (1913). *J. Physiol.* **46,** 173.

GAIRDNER, D., MARKS, J. & ROSCOE, J. D. (1954). *Lancet*, **2,** 1285.
GALLETI, P. M. & JOYET, G. (1958). *J. clin. Endocr.* **18,** 1102.
GARDNER, A. M. N. (1958). *Quart. J. Med.* **27,** 227.
GARROD, SIR ARCHIBALD (1908). *Lancet*, **2,** 1, 73, 142, 214.
GARRY, R. C. & WOOD, H. O. (1945-46). *Nutr. Abstr. Rev.* **15,** 591.
GARRY, R. C., PASSMORE, R., WARNOCK, G. M. & DURNIN, J. V. G. A. (1955). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 289.
GAVRILESCU, N., MEIKLEJOHN, A. P., PASSMORE, R. & PETERS, R. A. (1932). *Proc. roy. Soc. B.* **110,** 431.
GEIRINGER, E. (1950). *Rev. méd. Liège*, **5,** 614.
GELL, P. H. G. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 275, p. 193.
GEMMIL, J. S. & MANDERSON, W. G. (1960). *Lancet*, **2,** 307.
GERTLER, M. M., GARN, S. M. & WHITE, P. D. (1950). *Circulation*, **2,** 696.
GEYER, R. P. (1960). *Physiol. Rev.* **40,** 150.
GILES, C. & SHUTTLEWORTH, E. M. (1958). *Lancet*, **2,** 1341.
GILLANDERS, A. D. (1951). *Brit. Heart J.* **13,** 177.
GILLMAN, J. & GILLMAN, T. (1951). *Perspectives in Human Malnutrition.* New York : Grune & Stratton.
GILLMAN, T., HATHORN, M. & CANHAM, P. A. S. (1959). *Amer. J. Path.* **35,** 349.
GIRDWOOD, R. H. (1953). *Lancet*, **1,** 53.
—— (1956). *Quart. J. Med.* **25,** 87.
—— (1957). *Amer. J. dig. Dis.* **2,** 159.
—— (1960). *Adv. clin. Chem.* **3,** 235.
GODDEN, W. & THOMSON, W. (1939). *J. Soc. chem. Ind. Lond.* **58,** 81.
GOFMAN, J. W. (1959). *Coronary Heart Disease.* Oxford : Blackwell ; Springfield, Illinois : Thomas.
GOFMAN, J. W., GLAZIER, F., TAMPLIN, A., STRISOWER, B. & DE LALLA, O. (1954). *Physiol. Rev.* **34,** 589.
GOLDBERG, A. (1961). *Scot. med. J.* **6,** 607.
GOLDBERG, L. & SMITH, J. P. (1960). *Amer. J. Path.* **36,** 125.
GOLDBERGER, J., WHEELER, G. A., LILLIE, R. D. & ROGERS, L. M. (1928). *Publ. Hlth Rep. Wash.* **43,** 1385.
GOPALAN, C. (1946). *Indian med. Gaz.* **81,** 22.
—— (1958). *J. trop. Pediat.* **4,** 87.
—— (1962). *Bull. Wld Hlth Org.* **26,** 203.
GOPALAN, C. & SRKIKANTIA, S. G. (1960). *Lancet*, **1,** 954.
GORDON, E. S. (1960). *Amer. J. clin. Nutr.* **8,** 740.
GORDON, H. LEWIS, B., EALES, L. & BROCK, J. F. (1957). *Lancet*, **2,** 1299.
GORDON, R. S. (1957). *J. clin. Invest.* **36,** 810.
GORDON, R. S. & CHERKES, A. (1956). *J. clin. Invest.* **35,** 206.
GRÄSBECK, R. (1960). *Adv. clin. Chem.* **3,** 299.
GREEN, R. G., CARLSON, W. E. & EVANS, C. A. (1942). *J. Nutr.* **23,** 165.
GREENBAUM, A. L. (1953). *Biochem. J.* **54,** 400.
GREENWALD, I. (1955). *Amer. J. clin. Nutr.* **3,** 215.
GREEP, R. O. & TALMAGE, R. V. ed. (1961). *The Parathyroids.* Springfield, Ill. : Thomas.
GREER, M. A., ETTLINGER, M. G. & ASTWOOD, E. B. (1949). *J. clin. Endocr.* **9,** 1069.
GREIG, H. B. W. & RUNDE, I. A. (1957). *Lancet*, **2,** 461.
GROEN, J. (1937). *J. clin. Invest.* **16,** 245.

Gross, J. & Pitt-Rivers, R. (1952). *Lancet*, **1**, 439.

Gunasekera, D. B. & Mahadeva, K. (1957). *Ceylon med. J.* (n.s.), **4**, 81.

Gyorgy, P. (1954). *Amer. J. clin. Nutr.* **2**, 231.

Gyorgy, P. & Goldblatt, H. (1939). *J. exp. Med.* **70**, 185.

Hahn, P. F. (1943). *Science*, **98**, 19.

Halstead, S. B. (1961). *Amer. J. trop. Med.* **10**, 918.

Ham, A. W. & Leeson, T. S. (1961). *Histology*, 4th ed. London: Pitman.

Hammond, E. C. & Horn, D. (1954). *J. Amer. med. Ass.* **155**, 1316.

Hampson, J., Loraine, J. A. & Strong, J. A. (1960). *Lancet*, **1**, 1265.

Hanna, S., Harrison, M., MacIntyre, I. & Fraser, R. (1960). *Lancet*, **2**, 172.

Hansen, A. E., Haggard, M. E., Boelsche, A. N., Adam, D. J. D. & Wiese, H. F. (1958). *J. Nutr.* **66**, 565.

Hansen, J. D. L. (1956). *S. Afr. J. Lab. clin. Med.* **2**, 206.

—— (1961). In *Recent Advances in Human Nutrition*, p. 267, ed. J. F. Brock. London: Churchill.

Hansen, J. D. L., Howe, E. E. & Brock, J. F. (1956). *Lancet*, **2**, 911.

Harrington, C. R. (1926). *Biochem. J.* **20**, 293.

Harrington, C. R. & Barger, G. (1927). *Biochem. J.* **21**, 169.

Harris, H. (1957). In *Biochemical Lesions in Human Disease*, ed. R. H. S. Thompson & E. J. King. London: Churchill.

—— (1959). *Human Biochemical Genetics*. London: Cambridge University Press.

Harris, L. J. (1955). *Vitamins in Theory and Practice*, 4th ed. London: Cambridge University Press.

Harris, L. J., Passmore, R. & Pagel, W. (1937). *Lancet*, **2**, 183.

Harrison, M., Fraser, R. & Mullan, B. (1961). *Lancet*, **1**, 1015.

Hausberger, F. X. & Hausberger, B. C. (1957). *Anat. Rec.* **127**, 305.

Havard, C. W. H. (1961). *Brit. med. J.* **2**, 1756.

Hawthorn, J. (1959). *Proc. Nutr. Soc.* **18**, 44.

Heath, C. W. & Patek, A. J. (1937). *Medicine*, **16**, 267.

Hegsted, D. M., Moscoso, I. & Collazos, C. (1952). *J. Nutr.* **46**, 181.

Hehir, P. (1922). *Brit. med. J.* **1**, 865.

Helweg-Larsen, P. and 6 others (1952). *Acta med. scand.* Suppl. 274.

Hench, P. S. (1941). *J. Amer. med. Ass.* **116**, 453.

Hercus, C. E. & Purves, H. D. (1936). *J. Hyg. Camb.* **36**, 182.

Hervey, G. R. & McCance, R. A. (1952). *Proc. roy. Soc. B.* **139**, 527.

—— —— (1954). *Proc. Nutr. Soc.* **13**, 41.

Hilditch, T. P. (1956). *The Chemical Constitution of Natural Fats*, 3rd ed. London: Chapman & Hall.

Hill, K. R. (1952). *West Indian med. J.* **1**, 243.

Himsworth, H. P. (1950). *The Liver and its Diseases*, 2nd ed. Oxford: Blackwell.

Hindhede, M. (1913). *Scand. Arch. Physiol.* **28**, 165.

Hinton, J. J. C. (1948*a*). *Brit. J. Nutr.* **2**, 237.

—— (1948*b*). *Nature*, **112**, 913.

Hodgkin, D. C., Pickworth, J., Robertson, J. H., Trueblood, K. N. & Prosen, R. J. (1955). *Nature*, **176**, 325.

Holmes, E. G., Jones, E. R. & Stainier, M. W. (1954). *Brit. J. Nutr.* **8**, 173.

Holmes, E. G., Jones, E. R., Lyle, M. D. & Stanier, M. W. (1956). *Brit. J. Nutr.* **10**, 198.

Holt, L. E., Gyorgy, P., Pratt, E. L., Snyderman, S. E. & Wallace, W. M. (1960). *Protein and Amino Acid Requirements in Early Life*. New York: New York University Press.

Hope, T. C. (1798). *Trans. R. Soc. Edinb.* **4**, part 2, 3.

Hopkins, F. G. (1912). *J. Physiol.* **44**, 425.

—— (1942). *Proc. roy. Soc. B.* **130**, 359.

Horwitt, M. K., Harvey, C. C., Rothwell, W. S., Cutler, J. L. & Haffron, D. (1956). *J. Nutr.* **60**, Suppl. 1.

Howie, J. W. (1949). *Brit. J. Nutr.* **2**, 331.

Huang, Po-Chao & Tung, Ta-Chang (1955). *J. Formosan med. Ass.* **54**, 115.

Hume, E. M. & Krebs, H. A. (1949). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 264.

Hunter, D. (1955). *The Diseases of Occupation*. London: English Universities Press.

Hunter, W. W. (1868). *Annals of Rural Bengal*, p. 26. London.

Hurst, A. F. (1929). *Lancet*, **2**, 1023.

Hussain, R. & Patwardhan, V. N. (1959). *Lancet*, **1**, 1073.

Hutchinson, J. B., Moran, T. & Pace, J. (1959). *Brit. J. Nutr.* **13**, 151.

Hutner, S. H. & McLaughlin, J. J. A. (1958). *Sci. Amer.* **199**, 92.

Hytten, F. E. (1954). *Brit. med. J.* **1**, 249.

Illingworth, C. F. W. (1953). *Peptic Ulcer.* Edinburgh : Livingstone.

Illingworth, R. S. & Kilpatrick, B. (1953). *Lancet,* **2,** 1175.

Indian Council of Medical Research. Liver Disease Sub-Committee (1955). *Indian J. med. Res.* **43,** 725.

International Commission on Radiological Protection (1960). *Health Physics,* **3,** 1.

Irvine, W. J., Davies, S. H., Delamore, I. W. & Wynn Williams, A. (1962). *Brit. med. J.* **2,** 454.

Jackson, C. M. (1925). *The Effects of Inanition and Malnutrition upon Growth and Structure.* London : Churchill.

James, A. H. (1957). *The Physiology of Gastric Digestion.* London : Arnold.

James D. G. O. and 5 others (1961). *Lancet,* **2,** 798.

Jansen, B. C. P. & Donath, W. F. (1926). *Verh. kon. ned. Akad. Wet.* **29,** 1390.

Jehers, H. (1942). *New Eng. J. Med.* **277,** 221.

Jeliffe, D. B. (1952). *Brit. med. J.* **2,** 1131.

—— (1959). *J. Pediat.* **54,** 227.

Jelliffe, D. B. & Stuart, K. L. (1954). *Brit. med. J.* **1,** 75.

Jelliffe, D. B., Bras, G. & Stuart, K. L. (1954). *Ann. trop. Med. Parasit.* **48,** 386.

Jellinek, E. M. (1955). *Proc. Nutr. Soc.* **14,** 93.

Johnson, M. L., Burke, B. S. & Mayer, J. (1956). *Amer. J. clin. Nutr.* **4,** 37.

Johnson, R. E. & Sargent, F. (1958). *Proc. Nutr. Soc.* **17,** 179.

Joly, J. S. (1929). *Stone and Calculas Disease of the Urinary Organs.* London : Heinemann.

Jones, F. Avery (1957). *Brit. med. J.* **1,** 719, 786.

Jones, R. H. (1938). *J. R. statist. Soc.* **101,** 1.

Josey, W. E. (1954). *Amer. J. clin. Nutr.* **2,** 303.

Kanagaratnam, K., Boon, W. K. & Hoh, T. K. (1960). *Lancet,* **1,** 538.

Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N. & Stokes, J. (1961). *Ann. intern. Med.* **55,** 33.

Kark, R. M. (1953). *Proc. Nutr. Soc.* **12,** 279.

Karvonen, M. J., Rautanen, Y., Rikkonen, P. & Kihlberg, I. (1958). *Ann. med. intern. Fenn.* **47,** 75.

Karvonen, M. J., Orma, E., Keys, A., Fidanza, F. & Brozek, J. (1959). *Lancet,* **1,** 492.

Kaser, M. M., Steinkamp, R. C., Robinson, W. D., Patton, E. W. & Youmans, J. B. (1947). *Amer. J. Hyg.* **46,** 297.

Katz, L. N., Stamler, J. & Pick, R. (1959). *Nutrition and Atherosclerosis.* London : Kimpton ; New York : Lea & Febiger.

Kaunitz, H. (1956). *Nature,* **178,** 1141.

Kayahan, S. (1960). *Lancet,* **1,** 255.

Kekwick, A. & Pawan, G. L. S. (1956). *Lancet,* **2,** 155.

Kekwick, A., Pawan, G. L. S. & Chalmers, T. M. (1959). *Lancet,* **2,** 1157.

Kellar, R. J. (1962). In *Combined Textbook of Obstetrics and Gynaecology,* 7th ed., p. 335, ed. D. Baird. Edinburgh : Livingstone.

Kellog, F. & Mettjer, S. R. (1936). *Arch. intern. Med.* **58,** 278.

Kelly, F. C. & Sneddon, W. W. (1958). *Bull. Wld Hlth Org.* **18,** 5.

Kempner, W. (1945). *N. Carolina med. J.* **6,** 117.

Kemsley, W. F. (1952). *Ann. Eugen. Lond.* **16,** 316.

Kendall, E. C. & Osterberg, A. E. (1919). *J. biol. Chem.* **40,** 265.

Kennedy, G. C. (1950). *Proc. roy. Soc. B.* **137,** 535.

Kennedy, T. H. (1942). *Nature,* **150,** 233.

Kerr, D. N. S. & Davidson, L. S. P. (1958*a*). *Lancet,* **2,** 489.

—— —— (1958*b*). *Lancet,* **2,** 483.

Keys, A. (1953). *J. Mt. Sinai Hosp.* **20,** 118.

—— (1955). *Weight Control,* p. 23. A Symposium, ed. E. S. Eppright, P. Swanson & C. A. Iverson. Iowa : Iowa State College Press.

Keys, A. & Brozek, J. (1953). *Physiol. Rev.* **33,** 245.

Keys, A., Henschel, A., Taylor, H. L., Mickleson, O. & Brozek, J. (1945). *Amer. J. Physiol.* **144,** 5.

Keys, A., Brozek, J., Henschel, A., Michelsen, O. & Taylor, H. L. (1950). *The Biology of Human Starvation.* Minneapolis : University of Minnesota Press.

Keys, A., Anderson, J. T., Fidanza, F., Keys, M. H. & Swahn, B. (1955). *Clin. Chem.* **1,** 34.

Keys, A. and 5 others (1957). *Fed. Proc.* **16,** 204.

King, J. D., Mellanby, M., Stones, H. M. & Green, H. N. (1955). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. **288.**

Kinsell, L. W., Partridge, J., Boling, L., Margen, S. & Michaels, G. (1952). *J. clin. Endocr.* **12,** 909.

Kitchin, A. H., Passmore, R., Pyke, M. & Warnock, G. M. (1949). *Brit. J. soc. Med.* **3,** 10.

Knox, W. E. (1960). *Pediatrics,* **26,** 1.

Kodicek, E. (1940). *Biochem. J.* **34,** 712.

—— (1956). *Ann. Rev. Biochem.* **25,** 497.

Kodicek, E., Carpenter, K. J. & Harris, L. J. (1947). *Lancet,* **2,** 616.

Kodicek, E., Braude, R., Kon, S. K. & Mitchell, K. G. (1956). *Brit. J. Nutr.* **10,** 51.

Kon, S. K. & Cowie, A. T. (1961). *Milk: The Mammary Gland and its Secretion.* London: Academic Press.

Kon, S. K. & Mawson, E. H. (1950). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 269.

Korn, E. D. (1958). Lipoprotein Lipase. In *Chemistry of Lipids as Related to Atherosclerosis,* p. 169, ed. I. H. Page. Springfield, Illinois: Thomas.

Krahl, M. E. (1961). *The Action of Insulin on Cells.* New York & London: Academic Press.

Krebs, H. A. (1953). *Proc. Nutr. Soc.* **12,** 237.

—— (1961). *Biochem. J.* **80,** 225.

Krebs, H. A. & Kornberg, H. L. (1957). *Transformation in Living Matter.* Berlin: Springer.

Kuhn, R., Gyorgyi, P. & Wagner-Jauregg, T. (1933). *Ber. dtsch. chem. Ges.* **66,** 1034.

Kuppuswamy, S., Sreenivasam, M. & Subramanyan, V. (1958). *Indian Coun. med. Res. Spec. rep. Ser.* No. 33.

Lal, R. B. & Roy, S. C. (1937). *Indian J. med. Res.* **25,** 163.

Lal, R. B., Mukherji, S. P., Das Gupta, A. C. & Chatterji, S. R. (1940). *Indian J. med. Res.* **28,** 163.

Lambertsen, C. J., Kough, R. H., Cooper, D. Y., Emmel, G. L., Loeschek, H. H. & Schmidt, C. F. (1953). *J. appl. Physiol.* **5,** 471.

Lancaster, M. C., Jenkins, F. P. & Philp, J. McL. (1961). *Nature,* **192,** 1095.

Lancet (1956). **1,** 142.

—— (1961*a*). **2,** 1391.

—— (1961*b*). **1,** 1101.

—— (1961*c*). **1,** 809.

Landor, J. V. & Pallister, R. A. (1935). *Trans. R. Soc. trop. Med. Hyg.* **29,** 121.

Larsen, B. L. (1960). *J. Dairy Sci.* **43,** 1.

Larsen, D. L. & Tomlinson, L. J. (1952). *J. Lab. clin. Med.* **39,** 129.

Lawes, J. B. & Gilbert, J. H. (1853). *Report of the 22nd Meeting of the British Association for the Advancement of Science,* p. 323.

Lawrence, J. S. (1961). *Ann. rheum. Dis.* **20,** 11.

League of Nations Technical Commission on Nutrition (1936*a*). *Quart. Bull. Hlth Org. L. o. N.* **5,** 391.

—— (1936*b*). *Quart. Bull. Hlth Org. L. o. N.* **5,** extract No. 6.

—— (1938). *Bull. Hlth Org. L. o. N.* **7,** 460.

Le Breton, E. & Trémolières, J. (1955). *Proc. Nutr. Soc.* **14,** 97.

Lehmann, G., Müller, E. A. & Spitzer, H. (1950). *Arbeitsphysiologie,* **14,** 166.

Lehmann, H. (1949). *Trans. R. Soc. trop. Med. Hyg.* **43,** 199.

Leichenger, H., Eisenberg, G. & Carlson, A. J. (1948). *J. Amer. med. Ass.* **136,** 388.

Leitch, I. (1937). *Nutr. Abstr. Rev.* **6,** 553.

—— (1951). *Brit. J. Nutr.* **5,** 142.

Leithead, C. S., Guthrie, J., de la Place, S. & MacGraith, B. (1958). *Lancet,* **2,** 109.

Leitner, Z. A., Moore, T. & Sharman, I. M. (1952). *Brit. J. Nutr.* **6,** x.

Leone, N. C. and 6 others (1955). *Publ. Hlth Rep. Wash.* **69,** 925.

Leverton, R. M., Johnson, N., Pazur, J. & Ellison, J. (1956). *J, Nutr.* **58,** 219.

Levy, A. M. (1907). The Physiology of Metabolism. In *Metabolism and Practical Medicine,* ed. C. von Norden, vol. 1. London: Heinemann.

Lew, E. A. (1960). *Build and Blood Pressure Study,* 1959. Report to XVI International Congress of Actuaries, Brussels.

—— (1961). *J. Amer. diet. Ass.* **38,** 323.

Lien-Keng, K., Poesponegoro, S. D. & Seng Hin, P. (1957). *Docum. Med. geogr. trop. (Amst.),* **9,** 69.

Lightwood, R. (1952). *Proc. R. Soc. Med.* **45,** 401.

Lind, J. (1753). *A Treatise of the Scurvy.* Reprinted by Edinburgh University Press, 1953.

Link, K. P. (1944). *Fed. Proc.* **4,** 176.

Lipmann, F. (1954). In *Fat Metabolism,* p. 111. A symposium, ed. V. A. Najjar. Baltimore: John Hopkins Press.

Long, C. N. H. (1947). *Fed. Proc.* **6,** 461.

Lovern, J. A. (1957). *The Chemistry of Lipids of Biochemical Significance*, 2nd ed. London : Methuen.

Lucasse, C. (1952). *Ann. Soc. belge Méd. trop.* **32,** 391.

Ludford, R. J. (1954). *J. nat. Cancer Inst.* **6,** 89.

Lundsgaard, E. (1953). *Wld Hlth Org. Memo.* WHO/APD/ALC/7.

Lurie, A. O. & Jackson, W. P. U. (1962). *Clin. Sci.* **22,** 259.

Lusk, G. (1906). *The Science of Nutrition* (4th ed., 1928). Philadelphia & London: Saunders.

MacCallum, A. B. (1926). *Physiol. Rev.* **6,** 316.

McCance, R. A. (1936). *Lancet,* **1,** 823.

—— (1946). *Lancet,* **1,** 77.

—— (1950). *Amer. J. Med.* **9,** 229.

McCance, R. A. & Barrett, A. M. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 275, 83.

McCance, R. A. & Shipp, H. L. (1933). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 187.

McCance, R. A. & Widdowson, E. M. (1937). *Lancet,* **2,** 680.

—— —— (1942). *J. Physiol.* **101,** 44, 304.

—— —— (1951). *Proc. roy. Soc. B.* **138,** 115.

—— —— (1956). *Breads White and Brown.* London : Pitman.

—— —— (1960). *Spec. Rep. Ser. med. res. Coun. (Lond.),* No. 297.

McCance, R. A., Widdowson, E. M. & Shackleton, L. R. B. (1938). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 213.

McCance, R. A., Widdowson, E. M. & Lehmann, H. (1942). *Biochem. J.* **36,** 686.

McCance, R. A., Widdowson, E. M., Moran, T., Pringle, W. J. S. & Macrae, T. F. (1945). *Biochem. J.* **39,** 213.

McCarrison, R. (1908*a*). *Lancet,* **2,** 1275.

—— (1908*b*). *Indian med. Gaz.* **43,** 441.

—— (1919). *Studies of Deficiency Disease.* Oxford : Medical Publications.

—— (1936). *Nutrition and Health.* Cantor Lectures republished (1953). London : Faber.

McCarrison, R., Newcomb, C., Viswanath, R. & Norris, R. V. (1927). *Indian J. med. Res.* **15,** 197.

McCay, C. M. (1949). *Vitam. and Horm.* **7,** 147.

—— (1955). In *Colloquia on Ageing*, vol. 1, ed. G. E. W. Wolstenholme & M. P. Cameron. Ciba Foundation. London : Churchill.

McClellan, W. S. & Du Bois, E. F. (1930). *J. biol. Chem.* **87,** 651.

McCollum, E. V. & Davis, M. (1913). *J. biol. Chem.* **15,** 167.

McDonald, L. & Edgill, M. (1957). *Lancet,* **2,** 457.

Macfarland, M. L. & McHenry, E. W. (1948). *J. biol. Chem.* **176,** 429.

McGeown, M. G. & Bull, G. M. (1957). *Brit. med. Bull.* **13,** 53.

M'Gonigle, G. M. C. & Kirby, J. (1936). *Poverty and Public Health.* London : Gollancz.

Mackay, I. F. S., Patrick, S. J., Stafford, D. & Cleveland, F. S. (1956). *J. Nutr.* **59,** 155.

Maclagan, N. F. (1940). *Quart. J. Med.* **9,** 151.

—— (1957). *Brit. med. Bull.* **13,** 75.

McLester, J. S. & Darby, W. J. (1952). *Nutrition and Diet in Health and Disease*, p. 263. Philadelphia and London : Saunders.

McNair, T. J. & Dudley, H. A. F. (1959). *Lancet,* **2,** 365.

Macrae, T. F., Henry, K. M. & Kon, S. K. (1943). *Biochem. J.* **37,** 225.

Macy, I. G. (1949). *Amer. J. Dis. Childh,* **78,** 589.

Maddocks, I. (1961). *Lancet,* **2,** 396.

Magnus, H. A. (1952). In *Modern Trends in Gastroenterology*, Series I, p. 347, ed. F. Avery Jones. London : Butterworth.

—— (1958). *J. clin. Path.* **11,** 289.

Malm, O. J. (1953). *Scand. J. clin. Lab. Invest.* **5,** 75.

—— (1958). *Scand. J. clin. Lab. Invest.* **10,** suppl. 36.

Man, E. B. & Gildea, E. F. (1932). *J. biol. Chem.* **90,** 61.

Manchanda, S. S. & Gupta, H. L. (1959). *Indian J. Hlth,* **8,** 217.

Mann, C. V., Teel, K., Hayes, O., McNally, A. & Bruno, D. (1955). *New Engl. J. Med.* **253,** 349.

Mardones, R. J. (1951). *Quart. J. Stud. Alc.* **12,** 563.

Marine, D. (1924). *Medicine,* **3,** 453.

Marine, D. & Kimball, O. P. (1920). *Arch. intern. Med.* **25,** 661.

Marine, D. & Lenhart, C. H. (1911). *J. exp. Med.* **13,** 455.

Marrison, L. W. (1957). *Wines and Spirits.* Pelican Book A383. London : Penguin Books.

Masterton, T. P., Lewis, H. E. & Widdowson, E. M. (1957). *Brit. J. Nutr.* **11,** 346.

Mayer, J. (1953*a*). *Physiol. Rev.* **33,** 472.

—— (1953*b*). *New Engl. J. Med.* **249,** 13.

—— (1955). In *Weight Control*, p. 199, ed. E. S. Eppright, P. Swanson & C. A. Iverson. Iowa : Iowa State College Press.

—— (1960). *Amer. J. clin. Nutr.* **8,** 712.

Mayer, J. & Bullen, D. (1960). *Physiol. Rev.* **40,** 369.

Mayer, J., Marshall, N. B., Vitale, J. J., Christensen, J. H., Mashayekhi, M. B. & Stare, F. J. (1954). *Amer. J. Physiol.* **177,** 544.

Mears, E. (1961). *Brit. med. J.* **2,** 1179.

Medical Research Council (1947). *Report for the years* 1939-45. Cmd. **7335,** 110.

—— (1956). *Lancet,* **1,** 901.

—— (1961). *Brit. med. J.* **2,** 1143.

Meiklejohn, A. P. (1933). *Biochem. J.* **27,** 1310.

—— (1940). *New Engl. J. Med.* **223,** 265.

—— (1953). *Vitam. & Horm.* **11,** 61.

Meiklejohn, A. P., Passmore, R. & Stewart, C. P. (1953). In the reprint of Lind's *A Treatise of the Scurvy.* Edinburgh : The University Press.

Mellanby, E. (1918). *J. Physiol.* **52,** xi, liii.

—— (1921). *Spec. Rep. Ser. Med. res. Coun.* (*Lond.*), No. 61.

—— (1925). *Spec. Rep. Ser. Med. res. Coun.* (*Lond.*), No. 93.

—— (1934). *Nutrition and Disease.* Edinburgh : Oliver & Boyd.

—— (1950). *A Story of Nutritional Research.* Baltimore : Williams & Wilkins.

—— (1951). *Brit. med. J.* **2,** 863.

Mellanby, M. & Mellanby, H. (1954). *Brit. med. J.* **2,** 944.

Mellander, O., Vahlquist, B. & Melebin, T. (1959). *Acta Pædiat.* **48,** Suppl. 116.

Metropolitan Life Insurance Company (1960). *Statist. Bull.* 41 (Feb.) 6, (Mar.) 1.

Mettier, S. R., Minot, G. R. & Townsend, W. C. (1930). *J. Amer. med. Ass.* **95,** 1089.

Metz, J., Brandt, V. & Stevens, K. (1962). *Brit. med. J.* **1,** 24.

Meulengracht, E. (1939). *Brit. med. J.* **2,** 321.

Meyer, K. F. (1953). *New Engl. J. Med.* **249,** 843.

Miller, H. & Wilson, G. M. (1953). *Clin. Sci.* **12,** 97.

Miller, L. L. (1950). *J. biol. Chem.* **186,** 253.

Millis, J. (1952). *Med. J. Malaya,* **6,** 157.

Mills, A. R. (1956). *J. trop. Med. Hyg.* **59,** 99.

Ministry of Food (1954). *Food Standards Committee Report on Colouring Matters Recommendations relating to the Use of Colouring Matters in Foods.* London : H.M.S.O.

Ministry of Health, Scottish Office (1962). *Rep. publ. Hlth med. Subj.* (*Lond*), No. 105.

Minot, G. R. & Murphy, W. P. (1926). *J. Amer. med. Ass.* **87,** 470.

Minot, G. R., Strauss, M. B. & Cobb, S. (1933). *New Engl. J. Med.* **208,** 1244.

Mitchell, H. H. & Hamilton, T. S. (1929). *The Biochemistry of Amino Acids,* p. 556. New York : The Chemical Catalog Co. Inc.

Mitchell, H. K., Snell, E. E. & Williams, R. J. (1941). *J. Amer. chem. Soc.* **63,** 2284.

Mitchell, R. G. (1951). *Lancet,* **2,** 57.

Mitra, K. (1941). *Indian J. med. Res.* **29,** 143.

—— (1942). *Indian J. med. Res.* **30,** 91.

Model, W. (1960). *J. Amer. med. Ass.* **173,** 1131.

Montgomery, R. D. (1961). *J. Pediat.* **59,** 119.

Moore, C. V. (1961). *Harvey Lectures,* Series **55,** 67.

Moore, C. V. & Dubach, R. (1951). *Trans. Ass. Amer. Phycns,* **64,** 245.

—— —— (1955). In *Modern Trends in Blood Diseases,* pp. 109-133, ed. J. F. Wilkinson. London : Butterworth.

Moore, F. D. (1959). *The Metabolic Care of the Surgical Patient.* Philadelphia & London : Saunders.

Moore, T. (1957). *Vitamin A.* London and New York : Elsevier.

Moran, T. (1959). *Nutr. Abstr. Rev.* **29,** 1.

Morgan, A. D. (1956). *The Pathogenesis of Coronary Occlusion.* London : Oxford University Press.

Morris, J. N. & Crawford, M. D. (1958). *Brit. med. J.* **2,** 1485.

Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G. & Parke, J. W. (1953). *Lancet,* **2,** 1053, 1111.

Mosenthal, H. O. (1931). *The Diagnosis and Treatment of Variations in Blood-pressure and Nephritis.* New York : Oxford University Press.

Mottram, V. H. & Graham, G. (1956). *Hutchison's Food and the Principles of Dietetics,* 11th ed. London : Arnold.

Muehrcke, R. C. (1956). *Brit. med. J.* **1,** 1327.

Müller, E. A. & Franz, H. (1952). *Arbeitsphysiologie,* **14,** 499.

Murray, M. M., Ryle, J. A., Simpson, B. W. & Wilson, D. C. (1948). *M.R.C. Memo.* No. 18.

Murthy, H. B. N., Reddy, S. K., Swaminathan, M. & Subrahmanyan, V. (1955). *Brit. J. Nutr.* **9**, 203.

National Academy of Sciences (1961). *Meeting Protein Needs of Infants and Pre-School Children.* Proceedings of an International Conference. National Research Council Publication 843. Washington.

Nelson, J. W. (1953). *Trans. R. Soc. Med. Hyg.* **47**, 224.

Neuberger, A. & Sanger, F. (1942). *Biochem. J.* **36**, 662.

Nicol, B. M. (1939). *Lancet*, **3**, 881.

—— (1949). *Brit. J. Nutr.* **3**, 25.

—— (1952). *Brit. J. Nutr.* **6**, 34.

—— (1953). *Proc. Nutr. Soc.* **12**, 66.

—— (1956). *Brit. J. Nutr.* **10**, 275.

—— (1959). *Brit. J. Nutr.* **13**, 307.

Nicol, B. M. & Phillips, P. G. (1961). *Meeting Protein Needs of Infants and Pre-School Children.* National Academy of Sciences, National Research Council. Publication 843. Washington.

Nicholls, L. & Nimalasuriya, A. (1939). *J. Nutr.* **18**, 385.

Nicolaysen, R. & Eeg-Larsen, N. (1953). *Vitam. & Horm.* **11**, 29.

Nicolaysen, R., Eeg-Larsen, N. & Malm, O. J. (1953). *Physiol. Rev.* **33**, 424.

Nordin, B. E. C. (1961). *Lancet*, **1**, 1011.

Norris, T. (1949). Dietary Surveys: Their Technique and Interpretation. *Nutritional Studies*, No. 4. Washington: FAO.

Nutrition Society, Scottish Group (1957). *Proc. Nutr. Soc.* **16**, 135.

Oaks, W., Lisan, P. & Moyer, J. M. (1959). *Arch. intern. Med.* **104**, 527.

O'Brien, J. R. (1958). *Lancet*, **1**, 410

Ogston, D. & Fullerton, H. W. (1961). *Lancet*, **2**, 730.

Ohlson, M. A. and 10 others (1952). *Fed. Proc.* **11**, 775.

Olbrich, O. (1944). *Edinb. med. J.* **51**, 327.

Oldershaw, F. M. (1955). *Practitioner*, **174**, 690.

Oliver, M. F. (1960). In *Modern Trends in Cardiology*, ed. A. Morgan Jones. London: Butterworth.

—— (1962). *Lancet*, **1**, 653.

Oliver, M. F. & Boyd, G. S. (1953*a*). *Clin. Sci.* **12**, 217.

—— —— (1953*b*). *Brit. Heart J.* **15**, 387.

—— —— (1956). *Lancet*, **2**, 1273.

—— —— (1958). *Vitam. and Horm.* **16**, 147.

—— —— (1961). *Lancet*, **2**, 499.

Olson, R. E. & Vester, J. W. (1960). *Physiol. Rev.* **40**, 677.

Ooman, H. A. P. C. (1954). *Brit. J. Nutr.* **8**, 307.

—— (1958). *Fed. Proc.* **17**, Suppl. 2, iv.

Orr, J. B. (1936). *Food, Health and Income.* London: Macmillan.

Orr, J. B. & Gilks, J. L. (1931). *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 155.

Orr, M. L. & Watt, B. K. (1957). *Amino Acid Content of Foods.* Home Economics Research Report, No. 4. Washington.

Osborne, R. H., Adlersberg, D., de George, F. V. & Wang, C. (1959). *Amer. J. Med.* **26**, 54.

Osborne, T. B. & Mendel, L. B. (1913). *J. biol. Chem.* **15**, 311.

Oser, B. L. (1959). In *Protein and Amino Acid Nutrition*, p. 281, ed. A. A. Albanese. New York & London: Academic Press.

Owen, E. C. Irving, J. T. & Lyall, A. (1940). *Acta med. scand.* **103**, 235.

Page, E. W. & Page, E. P. (1953). *Obstet. and Gynec.* **1**, 94.

Pallister, R. A. (1952). *Med. J. Malaya*, **6**, 207.

Panel on Composition and Nutritive Value of Flour (1956). *Report of the Panel on Composition and Nutritive Value of Flour.* Cmd. 9757. London: H.M.S.O.

Pantin, C. F. A. (1931). *Biol. Rev.* **6**, 459.

Passmore, R. (1953). *Lancet*, **1**, 638.

—— (1961*a*). *Lancet*, **1**, 839.

—— (1961*b*). *Nutr. Dieta*, **3**, 1.

Passmore, R. & Durnin, J. V. G. A. (1955). *Physiol. Rev.* **35**, 801.

Passmore, R. & Ritchie, F. J. (1957). *Brit. J. Nutr.* **11**, 79.

Passmore, R., Thomson, J. G. & Warnock, G. M. (1952). *Brit. J. Nutr.* **6**, 253.

Passmore, R., Meiklejohn, A. P., Dewar, A. D. & Thow, R. K. (1955*a*). *Brit. J. Nutr.* **9,** 27.

—— —— —— —— (1955*b*). *Brit. J. Nutr.* **9,** 20.

Patterson, J. M. & McHenry, E. W. (1941). *Canad. J. publ. Hlth,* **32,** 362.

Patwardhan, V. N. (1952). *Nutrition in India.* Bombay : Hind Kitabs.

—— (1960). *Indian Coun. med. Rep. Spec. rep. Ser.* No 35.

Pawan, G. L. S. (1959). *Biochem. J.* **72,** 20 P.

Pedersen, P. O. (1947). *Proc. R. Soc. Med.* **40,** 726.

Peters, R. A. (1949). *Advanc. Sci.* **6,** No. 23, 257.

—— (1953). *Brit. med. Bull.* **9,** 116.

Peters, R. A. & Sinclair, H. M. (1933). *Biochem. J.* **27,** 1910.

Pett, L. B. (1955). *Canad. med. Ass. J.* **78,** 12.

Phansalkar, S. V. & Patwardhan, V. N. (1955). *Indian J. med. Res.* **43,** 265.

Phillips, G. B., Victor, M., Adam, R. D. & Davidson, C. S. (1952). *J. clin. Invest.* **31,** 859.

Philpot, F. J. & Pirie, A. (1943). *Biochem. J.* **37,** 250.

Pickering, G. W. (1961). *The Nature of Essential Hypertension.* London : Churchill.

Pigman, W. (1957). *The Carbohydrates.* New York : Academic Press.

Pincus, G. and 8 others (1959). *Science,* **130,** 81.

Pirie, A. & van Heyningen, R. (1956). *Biochemistry of the Eye.* Oxford : Blackwell.

Pirie, N. W. (1961). In *Penguin Science Survey* 1961-2, p. 70, ed S. A. Barnett & A. McLaren. London : Penguin Books.

—— (1962). *J. R. statist. Soc.* **A. 125,** 399.

Plagnol, H. & Dutrenit, J. (1956). *Med. trop. Marseilles,* **16,** 690.

Platt, B. S. (1955). *Proc. Nutr. Soc.* **14,** 115.

—— (1962). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 302.

Platt, B. S. & Fox, R. H. (1954). *Proc. Nutr. Soc.* **13,** 53.

Platt, B. S. & Gin, S. Y. (1934). *Trans. IX Congr. Far East Ass. trop. Med.* **2,** 407.

Platt, B. S. & Lu, G. D. (1936). *Quart. J. Med.* **5,** 355.

Platt, B. S. & Miller, D. S. (1959). *Proc. Nutr. Soc.* **18,** vii.

Ponseti, I. V. (1954). *J. Bone Jt. Surg.* **36,** 1031.

Poole, J. C. F. (1958). *Brit. med. Bull.* **14,** 253.

Popper, H. & Schaffner, F. (1957). *Liver & Structure and Function.* New York : McGraw Hill.

Porter, A. (1889). *The Diseases of the Madras Famine,* 1877-78. Madras : Government Press.

Postmus, S. (1958). *Trop. geogr. Med.* **10,** 363.

Pringle, J. M. D. (1947). *Listener,* **38,** 245.

Proceedings of the Nutrition Society (1961). **21,** 1.

Provis, H. S. & Ellis, R. W. B. (1955). *Arch. Dis. Childh.* **30,** 328.

Pugh, G. & Ward, M. (1953). In Sir John Hunt, *The Ascent of Everest,* p. 275. London : Hodder & Stoughton.

Pugh, L. G. C. (1954). *Proc. Nutr. Soc.* **13,** 60.

—— (1958). *J. Physiol.* **141,** 233.

Pyke, M. (1950). *Industrial Nutrition.* London : MacDonald & Evans.

—— (1952). *Townsman's Food.* London : Turnstile Press.

Rackemann, F. M. (1956). *The Inquisitive Physician : the Life and Times of George Richards Minot,* p. 125. Harvard : University Press.

Radhakrishna Rao, M. V. (1935). *Indian J. med. Res.* **23,** 69.

Ramalingaswami, V., Leach, E. H. & Sriramachari, S. (1955). *Quart. J. exp. Physiol.* **40,** 340.

Ramsbottom, J. (1953). *Proc. Nutr. Soc.* **12,** 39.

Ranganathan, S. (1938). *Indian J. med. Res.* **26,** 119.

Rao, K. S., Swaminathan, M. C., Swarup, S. & Patwardhan, V. N. (1959). *Bull. Wld Hlth Org.* **20,** 603.

Raoult, A., Thomas, J., Thiery, G., Perrin, G. & Perrellon, G. (1957). *Bull. méd. Afr. occid. franç.* (N.S.), **2,** 5.

Reh, E. (1962). Manual on Household Food Consumption Surveys. *Nutritional Studies,* No. 18. Rome : FAO.

Reissmann, K. R., Coleman, T. J., Budai, B. S. & Moriarty, L. R. (1955). *Blood,* **10,** 35.

Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R. & Folkers, K. (1948). *Science,* **107,** 396.

Ritchie, Jean (1950). Teaching Better Nutrition. *Nutritional Studies,* No. 6. Washington : FAO.

Robb, J. Marshall (1951). *Scotch Whisky : a Guide.* Edinburgh : Chambers.

Robinson, D. S. (1955). *Quart. J. exp. Physiol.* **40,** 112.

ROBINSON, D. S. & FRENCH, J. E. (1957). *Quart. J. exp. Physiol.* **42,** 151.
ROBINSON, H. E. (1959). *Nutr. Rev.* **17,** 257.
RODAHL, K. & MOORE, T. (1943). *Biochem. J.* **37,** 166.
RODGER, F. C. (1952). *Arch. Ophthal.* **47,** 570.
—— (1960). *Proc. Nutr. Soc.* **19,** 80.
ROHOLM, K. (1937). *Fluorine Intoxication.* London : Lewis.
ROLLESTON, H. D. (1932). *Medical Aspects of Old Age.* London : Macmillan.
ROSE, K. (1959). *Proc. Nutr. Soc.* **18,** 162.
ROSE, W. C., WIXOM, R. L., LOCKHART, H. B. & LAMBERT, G. F. (1955). *J. biol. Chem.* **217,** 987.
ROSENHEIM, O. & DRUMMOND, J. C. (1920). *Lancet,* **1,** 862.
ROWE, A. E. (1944). *Elimination Diets and the Patient's Allergies,* 2nd ed. Philadelphia : Lee & Febiger.
Royal Society of Health (1962). *Food Poisoning.* London : Royal Society of Health.
RUFFIN, J. M. & SMITH, D. T. (1934). *Amer. J. med. Sci.* **187,** 512.
RUSSELL, E. J. (1954). *World Population and World Food Supplies.* London : Allen & Unwin.
—— (1960). *New Scientist,* 21st July, 208.

SALAMAN, R. N. (1948). *History and Social Influence of the Potato.* Cambridge : University *Press.*
SALCEDO, J., BAMBA, M. D., CARASCO, E. O., JOSE, F. R. & VALENZUELA, R. C. (1948). *J. Philipp. med. Ass.* **25,** 519.
SARGEANT, K., ALLCROFT, R. & CARNAGHAM, R. B. A. (1961). *Vet. Rec.* **73,** 865.
SARKAR, S. N. (1948). *Nature,* **162,** 265.
SCHAEFER, L. E., ADLERSBERG, D. & STEINBERG, A. G. (1958). *Circulation,* **17,** 537.
SCHNIEDEN, H., HENDRICKSE, R. G. & HAIGH, C. P. (1958). *Trans. R. Soc. trop. Med. Hyg.* **52,** 169.
SCHNEIDER, H. A. (1946). *Vitam. & Horm.* **4,** 35.
SCHOENHEIMER, R. (1942). *The Dynamic State of Body Constituents,* p. 41. Cambridge, Mass. : Harvard University Press.
SCOTT, J. A. (1961). *Report on the Heights and Weights of School Pupils in the County of London in* 1959. London : L.C.C.
SCRIMSHAW, N. S. & BEHAR, M. (1961). *Science,* **133,** 2039.
SCRIMSHAW, N. S. & GUZMAN, M. A. (1953). *National Research Foundation. Nutrition Symposium Series,* No. 7, 110.
SCRIMSHAW, N. S., CABEZAS, A., CASTILLO, F. & MENDEZ, J. (1953). *Lancet,* **2,** 166.
SCRIMSHAW, N. S., TAYLOR, C. E. & GORDON, J. E. (1959). *Amer. J. med. Sci.* **237,** 367.
SCRIVER, C. R. (1960). *Pediatrics,* **26,** 62.
SEBRELL, W. H. & BUTLER, R. E. (1938). *Pub. Hlth Rep. Wash.* **53,** 2282.
SEBRELL, W. H. & HARRIS, R. S. ed. (1954). *The Vitamins : Chemistry, Physiology and Pathology.* New York : Academic Press.
SHAPER, A. G., JONES, M. & KYOBE, J. (1961). *Lancet,* **2,** 1324.
SHERLOCK, SHEILA (1958). *Diseases of the Liver and Biliary System,* 2nd ed. Oxford : Blackwell.
SHERMAN, H. C. (1920*a*). *J. biol. Chem.* **41,** 97.
—— (1920*b*). *J. biol. Chem.* **44,** 21.
—— (1941). *Chemistry of Food and Nutrition,* 6th ed., p. 253. New York : Macmillan.
SHORR, E. (1945). *J. Urol.* **53,** 507.
SIMPSON, I. A. & CHOW, A. Y. (1956). *J. trop. Pediat.* **2,** 3, 69.
SINCLAIR, H. M. (1953). *The Work of Sir Robert McCarrison.* London : Faber.
—— (1956). *Lancet,* **1,** 381.
—— (1962). *Proc. Nutr. Soc.* **21,** 1.
SINGH, A. & JOLLY, S. S. (1961). *Quart. J. Med.* **30,** 357.
SLEEMAN, W. H. (1844). *Rambles and Recollections of an Indian Official,* new edition (1893). Ed. by V. A. Smith, Westminster.
SMITH, D. A. & WOODRUFF, M. F. A. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.),* No. 274.
SMITH, E. B. (1960). *Lancet,* **1,** 799.
SMITH, E. L. & PARKER, L. F. J. (1948). *Biochem. J.* **43,** viii.
SMITH, H. G. (1954). *Proc. Nutr. Soc.* **13,** 45.
SMITH, H. V. & SPALDING, J. M. K. (1959). *Lancet,* **2,** 1019.
SMITH, H. W. (1951). *The Kidney.* New York : Oxford University Press.
SMITH, R. (1960). *Clin. Sci.* **19,** 275.
SNELL, E. E. & WRIGHT, L. D. (1941). *J. biol. Chem.* **139,** 675.
SOMESWARA, R. K., RAMANATHAN, M. K., TASKAR, A. D. & PHANSALKAR, S. V. (1955). *Indian J. med. Res.* **43,** 277.

Sommervell, T. H. & Orr, I. M. (1936). *Brit. J. Surg.* **24,** 227.

Soskin, S. & Levine, R. (1952). *Carbohydrate Metabolism*, 2nd ed. Chicago : University Press.

Spies, T. D., Milanes, F., Menéndez, A., Koch, M. B. & Minnich, V. (1946). *J. Lab. clin. Med.* **31,** 227.

Spillane, J. D. (1947). *Nutritional Disorders of the Nervous System.* Edinburgh : Livingstone.

Spillane, J. D. & Scott, G. I. (1945). *Lancet*, **2,** 261.

Spray, G. H. & Witts, L. J. (1959). *Lancet*, **2,** 702.

Stahmann, M. A., Huebner, C. F. & Link, K. P. (1941). *J. biol. Chem.* **138,** 513.

Stamler, J. and 8 others (1960). *Circulation*, **22,** 658.

Stefanik, P. A., Heald, F. P. & Mayer, J. (1959). *Amer. J. clin. Nutr.* **7,** 55.

Stein, H. & Isaacson, C. (1960). *Med. Proc.* **6,** 7.

Stetten, D. & Boxer, G. E. (1944). *J. biol. Chem.* **155,** 231.

Stewart, C. P. (1946). *Proc. Nutr. Soc.* **4,** 164.

Stewart, C. P., Scarborough, H. & Davidson, J. N. (1938). *Quart. J. Med.* **7,** 229.

Strominger, L. & Brobeck, J. R. (1953). *Yale J. Biol. Med.* **25,** 383.

Strong, J. A., Passmore, R. & Ritchie, F. J. (1958). *Brit. J. Nutr.* **12,** 105.

Stunkard, A. J. & McLaren Hume, M. (1959). *Arch. intern. Med.* **103,** 79.

Stunkard, A. J., Grace, W. J. & Wolff, H. G. (1955). *Amer. J. Med.* **19,** 78.

Sukatme, P. V. (1961). *J. R. statist. Soc. A.* **124,** 463.

Sutherland, A. B. (1955). *Proc. R. Soc. Med.* **47,** 995.

Swaminathan, M. (1937). *Indian J. med. Res.* **24,** 767.

—— (1938). *Nature*, **141,** 830.

Swanson, P., Roberts, H., Willis, E., Pesek, I. & Mairs, P. (1955). *Weight Control.* A symposium, ed. E. S. Eppright, P. Swanson & C. A. Iverson, p. 80. Iowa : Iowa College Press.

Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M. & Kruse, H. D. (1940). *J. Amer. med. Ass.* **114,** 2437.

Sydenstricker, V. P., Singal, S. A., Briggs, A. P., de Vaughn, N. M. & Isbell, H. (1942). *J. Amer. med. Ass.* **118,** 1199.

Takaki, K. (1885). *Sci-I Kwai, Trans.* **4,** suppl. 29.

—— (1906). *Lancet*, **1,** 1369, 1451, 1520.

Talbctt, J. H. (1957). *Metabolism*, **6,** 193.

Tasker, P. W. G. (1959). *Lancet*, **1,** 807.

Taylor, K. B. & Truelove, S. C. (1961). *Brit. med. J.* **2,** 924.

Taylor, K. B., Thomson, D. L., Truelove, S. C. & Wright, R. (1961). *Brit. med. J.* **2,** 1727.

Taylor, S. (1954). *J. clin. Endocr.* **14,** 1412.

Theron, J. J., Pretorius, P. L., Wolf, H. & Joubert, C. P. (1961). *J. Pediat.* **59,** 439.

Thomas, L. W. (1962). *Quart. J. exp. Physiol.* **47,** 179.

Thompson, J. C. (1946). *Proc. Nutr. Soc.* **4,** 171.

Thompson, M. D. & Trowell, H. C. (1952). *Lancet*, **1,** 1031.

Thompson, R. H. S. (1952). *Proc. R. Soc. Med.* **45,** 664.

—— (1957). In *Biochemical Disorders in Human Disease*, p. 420, ed. R. H. S. Thompson & E. J. King. London : Churchill.

Thompson, R. H. S. & Johnson, R. E. (1935). *Biochem. J.* **29,** 694.

Thompson, S. Y., Ganguly, J. & Kon, S. K. (1949). *Brit. J. Nutr.* **3,** 50.

Thomson, A. M. (1958). *Brit. J. Nutr.* **12,** 446.

—— (1959). *Brit. J. Nutr.* **13,** 509.

Thomson, A. M. & Billewicz, W. Z. (1957). *Brit. med. J.* **1,** 243.

Thomson, A. M. & Hytten, F. E. (1960). *Proc. Nutr. Soc.* **19,** 5.

Thomson, A. M., Billewicz, W. S. & Passmore, R. (1961). *Lancet*, **1,** 1027.

Thomson, J. (1954). *Hlth Bull. Edinb.* **12,** 25.

—— (1955). *Hlth Bull. Edinb.* **13,** 16.

Tompsett, S. L. (1934). *Biochem. J.* **28,** 1544.

Toor, M., Katchelsky, A., Agmon, J. & Allalouf, D. (1960). *Circulation*, **22,** 265.

Toverud, G. (1949). *Proc. R. Soc. Med.* **42,** 249.

Tower, D. B. (1956). *Amer. J. clin. Nutr.* **4,** 329.

Trant, H. (1954). *Lancet*, **2,** 703.

Trémolières, J. & Carré, L. (1959). *Rev. Alcool.* **5,** No. 3.

Trevelyan, G. M. (1942). *British Social History*, p. 341. London : Longmans Green.

Trowell, H. C. (1943). *Trans. R. Soc. trop. Med. Hyg.* **37,** 19.

Trowell, H. C., Davies, J. N. P. & Dean, R. F. A. (1954). *Kwashiorkor.* London : Arnold.

Truswell, A. S. & Brock, J. F. (1961). *Amer. J. clin. Nutr.* **9,** 715.

TULLOCH, J. A. (1962). *Diabetes Mellitus in the Tropics.* Edinburgh : Livingstone.
TURNER, J. W. A. (1955). *Lancet*, **1**, 661.
TUXFORD, A. W. (1942). *J. Hyg. Camb.* **42**, 549.

UNDERWOOD, E. J. (1953). In *Biochemistry and Physiology of Nutrition*, vol. 2, pp. 426-504, ed. G. H. Bourne & G. W. Kidder. London : Academic Books.
—— (1956). *Trace Elements in Human and Animal Nutrition.* London : Academic Books.
U.K. Mission (1953). *The Fluoridation of Water Supplies in North America as a Means of Controlling Dental Caries.* London : H.M.S.O.
United Nations (1954). *Population Growth and the Standard of Living in Underdeveloped Countries.* New York : UN Population Studies, No. 20.
UOTILA, U., RAEKALLIO, J. & EHRNROOTH, W. (1958). *Lancet*, **2**, 171.

VALLANCE-OWEN, J. (1960). *Brit. med. Bull.* **16**, 214.
VALLEE, B. L. & GIBSON, J. G. (1949). *Blood*, **4**, 455.
VAN DER SAR, A. (1951). *Docum, neerl. indones. Morb. trop.* **3**, 25.
VAN EEKELEN, M. & KOOY, R. (1933). *Acta brev. neerl. Physiol.* **3**, 169.
VAN SLYKE, D. D. MEYER, G. M. (1912). *J. biol. Chem.* **12**, 399.
VEDDER, E. B. (1913). *Beriberi.* London : Bale & Danielson.
VENKATACHALAM, P. S. (1962). *Bull. Wld Hlth Org.* **26**, 193.
VERNEY, E. B. (1957). *Lancet*, **2**, 1237, 1295.
VERZAR, F. & MCDOUGALL, E. J. (1936). *Absorption from the Intestine.* London : Longmans Green.

WALD, G. (1941). *J. opt. Soc. Amer.* **31**, 235.
WALKER, A. R. P. (1951). *Lancet*, **2**, 244.
—— (1954). *Nature*, **173**, 405.
WALKER, A. R. P. & ARVIDSSON, U. B. (1954). *Metabolism*, **3**, 385.
WALKER, A. R. P., FOX, F. W. & IRVING, J. T. (1948). *Biochem. J.* **42**, 452.
WALKER, A. R. P., ARVIDSSON, U. B. & DRAPER, W. L. (1954). *Trans. R. Soc. trop. Med. Hyg.* **48**, 395.
WALTER, R. (1748). *Lord Anson's Voyage Round the World*, 1740-44. Abridged and annotated by S. W. C. Pack. London : Penguin Books, 1947.
WALTERS, J. H. (1953). *Quart. J. Med.* **22**, 195.
WALTERS, J. H. & WATERLOW, J. C. (1954). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 285.
WARBURG, O. & CHRISTIAN, W. (1932). *Biochem. Z.* **254**, 438.
WATERLOW, J. C. (1961). *Proc. roy. Soc. B.* **155**, 96.
WATERLOW, J. C. & BRAS, G. (1957). *Brit. med. Bull.* **13**, 107.
WATERLOW, J. C. & MENDES, C. B. (1957). *Nature*, **180**, 1361.
WATERLOW, J. C. & WEISZ, T. (1956). *J. clin. Invest.* **35**, 346.
WATERLOW, J. C., CRAVIOTO, J. & STEPHEN, J. M. L. (1960). *Advanc. Protein Chem.* **15**, 131.
WATT, B. K. & MERRILL, A. L. (1950). *Composition of Foods.* Bureau of Human Nutrition and Home Economics. U.S. Dept. Agr. Handbook No. 8. Washington.
WEIJERS, H. A. (1950). *Thesis.* University of Utrecht.
WEIR, J. B. DE V. (1952). *Brit. J. Nutr.* **6**, 19.
WEISBERG, H. F. (1953). *Water, Electrolyte and Acid-base Balance*, p. 20. Baltimore : Williams & Wilkins.
WEISS, S. (1940). *J. Amer. med. Ass.* **115**, 832.
WERTHEIMER, E. & SHAPIRO, B. (1948). *Physiol. Rev.* **28**, 451.
WHELEN, W. S., FRASER, D., ROBERTSON, E. C. & TOMCZAEK, H. (1958). *Canad. med. Ass. J.* **78**, 177.
WHIPPLE, G. H. (1956). *Dynamic Equilibrium of Body Proteins.* Springfield, Ill. : Thomas.
WHITEHEAD, T. P. & PRIOR, A. P. (1960). *Lancet*, **2**, 1343.
WHYTE, H. M. (1958). *Aust. Ann. Med.* **7**, 36.
WIDDOWSON, E. M. (1955). *Proc. Nutr. Soc.* **14**, 142.
WIDDOWSON, E. M. & MCCANCE, R. A. (1943). *Lancet*, **1**, 230.
—— —— (1954). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 287.
WIDDOWSON, E. M. & THRUSSELL, L. A. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 275.
WIDDOWSON, E. M., MCCANCE, R. A. & SPRAY, C. M. (1951). *Clin. Sci.* **10**, 113.
WIDDOWSON, E. M., SLATER, J. E., HARRISON, G. E. & SUTTON, A. (1960). *Lancet*, **2**, 941.
WILKINSON, A. W. (1960). *Body Fluids in Surgery*, 2nd ed. Edinburgh : Livingstone.
—— (1961). *Lancet*, **2**, 783.
WILLIAMS, C. D. (1933). *Arch. Dis. Childh.* **8**, 423.

—— (1954*a*). *Report on Vomiting Sickness in Jamaica.* Kingston, Jamaica : Government Printer.
—— (1954*b*). *Lancet*, **1**, 323.
—— (1958). *W. Afr. med. J.* **7**, 5.
—— (1962). *Lancet*, **2**, 342.
WILLIAMS, R. D., MASON, H. L., SMITH, B. F. & WILDER, R. M. (1942). *Arch. intern. Med.* **69**, 721.
WILLIAMS, R. H. (1943). *New Engl. J. Med.* **228**, 247.
WILLIAMS, R. J. (1939). *Science*, **89**, 486.
—— (1956). *Biochemical Individuality*, pp. 135-165. New York : Wiley.
—— (1961). *Towards the Conquest of Beriberi.* Cambridge, Mass. : Harvard University Press.
WILLIAMS, R. R. & CLINE, J. K. (1936). *J. Amer. chem. Soc.* **58**, 1504.
WILLIAMSON, A. D. & LEONG, P. C. (1949). *Med. J. Malaya*, **4**, 83.
WILLS, L. (1931). *Brit. med. J.* **1**, 1059.
—— (1933). *Lancet*, **1**, 1283.
WILLS, V. G. & WATERLOW, J. C. (1958). *J. trop. Ped.* **3**, 167.
WILSON, D. C. (1929). *Indian J. med. Res.* **17**, 338, 881, 903.
WILSON, H. E. C. & GHOSH, B. K. (1937). *Indian med. Gaz.* **72**, 147.
WILSON, W. H. (1921). *J. Hyg. Camb.* **20**, 1.
WINEGRAD, A. I. & RENOLD, A. E. (1958). *J. biol. Chem.* **233**, 267.
WINTROBE, M. M. (1956). *Clinical Hæmatology*, 4th ed., p. 773. London : Kimpton.
WOLBACH, S. B. (1953). *Proc. Nutr. Soc.* **12**, 247.
WOLBACH, S. B. & HOWE, P. R. (1925). *J. exp. Med.* **42**, 753.
WOLBACH, S. B. & MADDOCK, C. L. (1952). *Arch. Path.* **53**, 54.
WOLFF, H. S. (1958). *Quart. J. exp. Physiol.* **43**, 270.
WOODRUFF, A. W. (1949). *Trans. roy. Soc. trop. Med. Hyg.* **42**, 605.
—— (1961). In J. F. Brock, *Recent Advances in Human Nutrition*, p. 415. London : Churchill.
WOOLEY, D. W. (1947). *Physiol. Rev.* **27**, 308.
WOOLF, B. (1954). *Proc. nutr. Soc.* **13**, 82.
World Health Organisation (1953). *Bull. Wld Hlth Org.* **9**, 293.
—— (1958). *Tech. Rep. Ser. Wld Hlth Org.* No. 143.
—— (1959). *Tech. Rep. Wld Hlth Org.* No. 182.
—— (1961). *Epidem. vit. Stat. Rep.* **14**, 510.
—— (1962*a*). *World Health*, January-February, p. 4.
—— (1926*b*). *Epidem. vit. Stat. Rep.* **15**, 89.
WRIGHT, A. S., PITTS, G. A. J. & MORTON, R. A. (1959). *Lancet*, **2**, 594.

YERUSHALMY, J. & HILLEBOE, H. E. (1957). *N.Y. med. J.* **57**, 2343.
YOUNG, A. (1771). *The Farmer's Tour through the East of England*, vol 4, p. 120. London.
YOUNG, C. M. & MCHENRY, E. W. (1942). *Canad. J. publ. Hlth*, **33**. 224.
—— (1943). *Canad. J. publ. Hlth*, **34**, 367.
YOUNG, F. G., BROOM, W. A. & WOLFF, W. F. eds. (1960). *The Mechanism of Action of Insulin.* Oxford : Blackwell.
YOUMANS, J. B. (1936). *Int. Clin.* **4**, 120.
—— (1957). *J. med. Ass. Ala.* **26**, 161.
YUDKIN, J. (1957). *Lancet*, **2**, 155.

ZIMMERMANN, B., CASEY, J. H., BLOCK, H. S., BICKEL, E. Y. & GORVIK, K. (1956). *Surg. Forum* **6**, 3.
ZOMZELY, C. & MAYER, J. (1959). *Amer. J. Physiol.* **196**, 956.
ZUELZER, W. W. & OGDEN, F. N. (1946). *Amer. J. Dis. Child.* **71**, 211.
ZUNTZ, N. (1897). *Pflüg. Arch. ges. Physiol.* **68**, 191.

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